A PILOT PROSPECTIVE CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LARGE-SCALE FIELD-DIRECTED TOPICAL THERAPY OF ACTINIC KERATOSIS OF THE CHEST WITH INGENOL MEBUTATE 0.015%

Protocol Number: PICATO-2013-01

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PROTOCOL VERSION: March 17, 2014 – Final

The study will be conducted according to the protocol and in compliance with International Conference of Harmonization Good Clinical Practice Guidelines and all other applicable regulatory requirements.

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PROTOCOL SIGNATURE PAGE

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PROTOCOL VERSION: March 17, 2014 – Final

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PROTOCOL SYNOPSIS

Protocol Title: A Pilot Prospective Clinical Trial to Evaluate the Efficacy and Safety of Large-Scale, Field-Directed Topical Therapy of Actinic Keratosis of the Chest with Ingenol Mebutate 0.015%

Protocol Number: PICATO-2013-01

Principal Investigator: Mitchel P. Goldman, MD

Study Duration: Seven (7) scheduled in-office visits over a 59-day period. Visits will be conducted at days 0, 1, 3, 10, 17, 24 and 59.

Study Population: Twenty (23) eligible male or female subjects 18 years of age or older with the presence of 4 or more actinic keratosis in one continuous 100cm^2 area of the chest.

Investigational Product (IP): Ingenol mebutate gel, 0.015% (Picato®, LEO Pharma, Parsippany, NJ).

Study Design: This will be an open-label study to evaluate the efficacy and safety of ingenol mebutate gel, 0.015% used as topical therapy for actinic keratosis on the chest. Subjects that present with 4 or more actinic keratosis in one continuous 100cm^2 area of the chest and meet all inclusion/exclusion criteria will be enrolled into this study.

Treatment with the investigational product (IP) will be applied for three continuous days. The investigator will guide application of the IP in-office at Day 0 and the subject will be instructed to self-administer the IP at Days 1 and 2. Follow-up visits will be scheduled at Days 1, 3, 10, 17, 24 and 59.

Prior to treatment the investigator will assess the subject's treatment area for lesion counts and appearance of photodamage/skin aging. At follow-up visits, subjects will be evaluated for lesion clearance at (visits 4, 5, 6 and 7), local skin reaction and changes in appearance of photodamage/skin aging using defined scales.

Photography will also be collected pre-treatment at Baseline and at each follow up visit.

During the treatment phase, application of the study drug will be administered at days 0 (investigator guided), 1 and 2 (home application by subject). For the follow-up phase, follow-up visits will be conducted at days 1, 3, 10, 17, 24 and 59.

1. BACKROUND AND RATIONALE

Actinic keratosis are common, premalignant lesions in light-skinned individuals found on the face, chest, and upper extremities that result from chronic, cumulative ultraviolet exposure and over time may progress to invasive squamous cell carcinoma [1,2]. Lesion-directed treatment, usually via cryosurgery, is limited by the potential for scarring and significant recurrence rates [2,3]. Topical, field-directed therapies (imiquimod, fluorouracil, and diclofenac) allow for the treatment of entire photodamaged areas, targeting clinically visible and subclinical lesions concurrently. However, the need for a prolonged course of treatment associated with sustained local reactions and poor patient compliance has classically limited the effectiveness of topical, field-directed therapies [2,4].

Ingenol mebutate gel (Picato, Leo Pharma, Parsippany, NJ) derived from the sap of the Euphorbia peplus plant is a novel topical, field-directed therapy for actinic keratosis in facial and non-facial sites [2,4-7]. The destruction of actinic keratosis is mediated by rapid lesion necrosis and subsequent lesion-specific, neutrophil-mediated, antibody-dependent cellular cytotoxicity [6]. Ingenol mebutate gel 0.015% applied once daily to the face for 3 consecutive days is an effective field-directed treatment for actinic keratosis demonstrating clearance rates comparable to other topical therapies with the advantage of rapid resolution of local cutaneous reactions and high patient compliance [4,5]. The local cutaneous reactions in the largest randomized-controlled trial of ingenol mebutate gel for actinic keratosis to date peaked on day 4 (application on days 1-3), were nearly resolved by day 15, and returned to baseline by day 29 [2].

Field-directed application of ingenol mebutate to contiguous areas is essential to target both clinically observable and subclinical lesions. Prior studies have only treated areas as large as 25 cm^2 [8]. We aim to evaluate the efficacy and safety of ingenol mebutate applied to contiguous areas of the chest as large of 100 cm^2.

2. STUDY OBJECTIVE

The primary efficacy endpoint will be complete clearance of all clinically visible AKs and no development of any new AKs on day 59. Lesion clearance will be determined on day 59 (visit 7) by comparing pretreatment lesion count with current lesion count on day 59, with primary efficacy endpoint being clearance of all lesions in treatment field and no growth of new lesions.

Secondary efficacy endpoints (all at day 59) will include stratification of patients into groups based on percent clearance. If patient is not found to have 100% clearance, total number of lesions present in the treatment field will be counted and percent clearance will be calculated. The percent clearance calculated, will then be used to defined what patients response as defined by defined percentage grading scale: complete clearance (no clinically evident residual disease and no new lesions), partial clearance (≥75% lesion clearance), mild clearance (10 to 74% lesion clearance), minimal to no clearance (<10%), worsened (clinically observable growth), or unable to be assessed.

The number of clinically observable AKs within the treatment area will be documented at baseline and at follow-up visits 2, 3, 4, 5, 6 and 7.

Subject satisfaction will also be assessed at visits 4, 5, 6 and 7 with a 7-point scale (0= Completely Dissatisfied, 1= Moderately Dissatisfied, 2= Mildly Dissatisfied, 3= Neither Dissatisfied Nor Satisfied (Neutral), 4= Mildly Satisfied, 5= Moderately Satisfied, 6= Completely Satisfied).

Secondary efficacy endpoints will also grade changes in photodamaged/skin aging in the following categories: Dyschromia, Erythema (E), Telangiectasia (T), Keratosis, Texture and Rhytides as compared to baseline and follow-up visits 6 and 7 using an 8-point grading scale with 0 indicating no presence and 4 indicating a severe presence. (Please see attached Modified Alexiades-Armenakas Comprehensive Grading Scale of Skin Aging for reference.)

Safety endpoints will be documented at each subject visit by the investigator. Local skin reactions will be evaluated quantitatively with the use of a clearly defined grading scale with a photographic guide to ensure consistent recording. The scale will range from 0 to 4 (based on increasing severity) for the following criteria: erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration. Other adverse events and any evidence of scarring in the treatment field will also be assessed and documented at each subject visit.

Demographic data and study variables will be analyzed by appropriate statistical methods.

3. STUDY DESIGN

This will be an open-label study to evaluate the efficacy and safety of ingenol mebutate gel, 0.015% used in topical therapy of actinic keratosis on the chest. Subjects that present with 4 or more actinic keratosis in one continuous 100cm^2 area of the chest and meet all inclusion/exclusion criteria will be enrolled into this study.

Treatment with the investigational product (IP) will be applied for three continuous days. The investigator will guide application of the IP in-office at Day 0 and the subject will be instructed to self-administer the IP at Days 1 and 2. Follow-up visits will be scheduled at Days 1, 3, 10, 17, 24 and 59.

Prior to treatment and at each visit, the investigator will assess the subject's treatment area for lesion counts and at follow up visits 4, 5, 6 and 7 evaluation of clearance. Pre-treatment photography will also be collected at baseline and at each follow up visit.

4. STUDY POPULATION

4.1 NUMBER

Twenty (23) eligible Male or female subjects 18 years of age or older with the presence of 4 or more actinic keratosis in one continuous 100cm^2 area of the chest.

4.2 INCLUSION CRITERIA

1. Male or female of at least 18 years of age.
2. Subjects willing to comply with study requirements.
3. The presence of four or more clinically typical actinic keratosis within one contiguous area of the chest that is 100cm^2.
4. For female subjects of childbearing potential willing to use an acceptable form of birth control during the entire course of the study. All systemic birth control measures must be in consistent use **at least 30 days prior to entry** into the study.

   A female is considered NOT to be of childbearing potential if she is postmenopausal for **at least one (1) year,** without a uterus, without both ovaries or has had a bilateral tubal ligation.

   Acceptable methods of birth control are: oral contraceptives, contraceptive patches/rings/implants Norplant, Depo-Provera, double-barrier methods (e.g. condoms and spermicide) and abstinence.

5. Subjects willing to refrain from the use of topical products containing alpha-hydroxy acids, retinoic acid, retinol, salicylic acid, and vitamins C/D (or their derivatives) in the treatment area 7 Days prior to and during the entire study period

4.3 EXCLUSION CRITERIA

1. Known hypersensitivity, prior allergic reaction, or prior chest treatment with ingenol mebutate gel.
2. Treatment area containing hypertrophic or hyperkeratotic lesions, cutaneous horns or lesions that had previously not responded to other standard treatments.
3. Presence of any skin condition or disease that might interfere with the diagnosis and evaluation of study parameters (i.e., atopic dermatitis, eczema, psoriasis, seborrheic dermatitis).
4. Subjects receiving ablative laser treatments on their chest must have discontinued the treatment **at least 6 months prior to entering** the study.
5. Subjects receiving Intense Pulse Light treatments on their chest must have discontinued the treatment **at least 30 days prior to entering** the study.

6. **Within 3 months of study entry** treatments that may interfere with evaluation of the treatment area (e.g. other topical therapies for actinic keratosis of the chest, topical corticosteroids, topical retinoids, ultraviolet B phototherapy, or immunosuppressive, immunomodulating, or cytotoxic medications) or expected use of any of the above-mentioned therapies in the treatment area listed during the duration of the study.
7. **Within 3 months of study entry** topical treatment in the treatment area for actinic keratosis including, but not limited to imiquimond, 5- fluorouracil, diclofenac or liquid nitrogen.
8. **Within 6 months of study entry** treatments with Poly-L-lactic acid (PLLA; Sculptra Aesthetic) that may interfere with the evaluation of the treatment area.
9. **Within 7 days of study entry** use of self-tanners, excessive exposure to sunlight or artificial UV light (e.g.: use of tanning beds/booths and/or sunbathing) or expectations of any listed during the time of the study within the treatment area.
10. Any systemic disease that is not yet stabilized for **at least six (6) Months prior to entering** study.
11. A significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would interfere with the objectives of the study
12. Pregnant or nursing women or women planning a pregnancy during the study period.
13. Any unhealed skin lesions or wounds within the treatment area.
14. Existence of one (1) or more suspected basal cell carcinoma or squamous cell carcinoma within the treatment area.
15. Current participation or participation **within 30 days prior to the start of this study** in a drug or investigational device research study.

5. MATERIALS AND METHODS

5.1 PRODUCT

- Ingenol Mebutate Picato® gel is an inducer of cell death indicated for the topical treatment of Actinic Keratosis

5.2 APPLICATION OF THE STUDY PRODUCT

At visit 1 Day 0, an Investigator will use placebo samples supplies by LEO Pharma to demonstrate to the subject the correct method of application. The Investigator will then watch the subject apply the first treatment in office. For subject home product application (See Appendix G)

6. SCHEDULE OF EVENTS

6.1 Schedule of Visits

VISIT	1	2	3	4	5	6	7
DAY	0	1	3 +/-1	10 +/-2	17 +/-3	24 +/-3	59 +/- 5
INFORMED CONSENT AND PHOTO RELEASE	X						
INCLUSION/EXCLUSION CRITERIA	X						
REVIEW MEDICAL HISTORY AND CONCURRENT MEDS	X						
INVESTIGATOR ASSESSMENT OF LESION COUNT	X	X	X	X	X	X	X
INVESTIGATOR - EVALUATION OF TREATMENT AREA CLEARANCE				X	X	X	X
INVESTIGATOR LOCAL SKIN RESPONSE GRADING		X	X	X	X	X	X
INVESTIGATOR - EVALUATION OF PHOTODAMAGE	X					X	X
INVESTIGATOR GUIDED APPLICATION OF THE INGENOL MEBUTATE (B)	X						
PHOTOGRAPHS(A)	X(A)	X	X	X	X	X	X
PREGNANCY TEST (IF APPLICABLE)	X						X
SUBJECT TSQM QUESTIONNAIRE			X				X
SUBJECT SATISFACTION QUESTIONNAIRE				X	X	X	X
DISPENSATION OF INGENOL MEBUTATE AND SUBJECT INSTRUCTIONS FOR HOME APPLICATION(C)	X(C)						
SUBJECT REVIEW OF HOME INGENOL MEBUTATE APPLICATION		X	X				
REVIEW OF ADVERSE EVENTS		X	X	X	X	X	X
REVIEW OF CONCOMMITANT MEDICATIONS		X	X	X	X	X	X

A. One (1) photo to be done Pre-treatment, Post-marking of treatment area.

B. See Section 5.3

C. See Appendix D

6.2 Study Period

Screening (Baseline, Day 0)

A prospective subject is to be examined to determine if they qualify for entry into the study. This initial examination will include:

- Obtain written Informed Consent, HIPPA and photographic release
- Review of Inclusions Exclusions Criteria
- Review of Medical History and Concomitant Medications
- Investigator Assessment of Lesion Count
- Investigator - Evaluation of Photodamage
- Urine Pregnancy Test (if applicable)
- Photography (Pre-Treatment Application - after markings)
- Investigator guided Application of the ingenol Mebutate
- Dispensation of Ingenol Mebutate and Subject Instructions for home application

Each qualified subject as they are enrolled in to the trial will be sequentially assigned a Subject ID number. Each subject will be instructed to return to the investigator's office, for follow-up visits at days 1, 3, 10, 17, 24 and 59 following the baseline visit.

The subject will be instructed to return in 1 Day for their next scheduled visit

Visit 2 (Day 1) *This follow-up examination will include:*

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Photography
- Subject review of home Ingenol Mebutate application
- Review of Adverse Events
- Review of Concomitant Medications

The subject will be instructed to return in 3 Days +/- 1 for their next scheduled visit

Visit 3 (Day 3 +/- 1) *This follow-up examination will include:*

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Photography
- Subject TSQM Questionnaire
- Subject review of home Ingenol Mebutate application
- Review of Adverse Events
- Review of Concomitant Medications

The subject will be instructed to return 10 Days +/- 2 From Baseline for their next scheduled visit

Visit 4 (Day 10 +/- 2) *This follow-up examination will include:*

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Investigator - Evaluation of Treatment area Clearance
- Photography
- Subject Satisfaction Questionnaire
- Review of Adverse Events
- Review of Concomitant Medications

The subject will be instructed to return 17 Days +/- 3 from Baseline for their next scheduled visit

Visit 5 (Day 17 +/- 3) *This follow-up examination will include:*

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Investigator - Evaluation of Treatment area Clearance
- Photography
- Subject Satisfaction Questionnaire
- Review of Adverse Events
- Review of Concomitant Medications
-

The subject will be instructed to return 24 Days +/-3 from Baseline for their next scheduled visit

Visit 6 (Day 24 +/- 3) *This follow-up examination will include:*

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Investigator - Evaluation of Treatment area Clearance
- Investigator - Evaluation of Photodamage
- Photography
- Subject Satisfaction Questionnaire
- Review of Adverse Events
- Review of Concomitant Medications
-

The subject will be instructed to return 59 Days +/-5 from Baseline for their next scheduled visit

Visit 7 (Day 59 +/- 5) - Final Visit

- Investigator Assessment of Lesion Count
- Investigator Local Skin Response Grading
- Investigator - Evaluation of Treatment area Clearance
- Investigator - Evaluation of Photodamage
- Urine Pregnancy Test (if applicable)
- Photography
- Subject TSQM Questionnaire
- Subject Satisfaction Questionnaire
- Review of Adverse Events
- Review of Concomitant Medications

6.3 STUDY ENDPOINT CRITERIA

a. Subject Completion of Study

If a subject has completed the final visit (Visit 7) of the study, they are considered to have completed the study.

b. Subject Discontinuation

Each subject may voluntarily discontinue the study at any time they choose. Subjects who cannot complete the study for any reasons (e.g., non-compliance, failure to meet visit schedule, etc.) will be discontinued from the study**.** These subjects will be asked to return for completion of visit 7.

c. Study Termination

The investigator with appropriate notification may terminate the study. If, after clinical observations, the investigator feels that it may be unwise to continue the study, he or she may stop the study.

6.4 Potential Risks and Benefits

A. Possible adverse events from Ingenol Mebutate treatment (during, immediately following treatment and possibly several weeks after)

- Erythema and inflammatory response
- Soreness/Pain
- Edema
- Infection
- Changes in skin pigmentation
- Flaking/Scaling
- Erosion/Ulceration
- Blistering
- Pruritus

B. **Serious and/or Adverse Events and Reporting**

A ***serious adverse event*** is any untoward medical occurrence, that:

- Results in death;
- is life-threatening;
- requires in-subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or is an important medical event.

An ***unexpected adverse event*** is any treatment-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test product.

Any serious adverse event occurring in this study must be reported to the IRB within 24 hours of awareness of the event. Initial reports must be made by telephone, followed by the completion of a Serious Adverse Event Report and submission by facsimile.

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An ***adverse event*** is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

All adverse events, including serious and treatment related or unexpected adverse events, must be recorded by the Investigator. Serious and unexpected device-related adverse events should be reported immediately to ThermiAesthetics.

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values, have either returned to normal or are otherwise explained.

If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

C. Unknown/Unforeseeable Risks

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with Subjects will be informed both verbally and in writing in a timely manner of any new information, findings or changes to the way the research will be performed that might influence their willingness to continue their participation in this study.

***Pregnancy/Fetal Risks*:** The effects of have not been studied in pregnancy and therefore **may be hazardous.**

If a subject becomes pregnant, the study doctor will refer the subject to seek obstetric care and will request to track the pregnancy to term. We will report the pregnancy to the Sponsor and IRB.

D. Benefits of Ingenol Mebutate

Ingenol Mebutate is FDA approved for the topical treatments of actinic keratosis.

7. Data Handling and Record Keeping

7.1 Data Handling and Record Keeping

The Investigator must ensure that proper source documentation for all study activities are diligently maintained and securely kept. The Investigator will sign the source documents for completeness, accuracy and integrity of the data collected. The Investigator will maintain reliable study Medication/Device dispensing/dosing records and will store study supplies in a secure, locked location. In

addition, the Investigator will ensure that all study-related source documentation will be maintained for a period of two years after the conclusion of the study.

8. Regulatory Obligations

8.1 Institutional Review Board

The study protocol, informed consent forms (all versions), and any specific advertising will be submitted to and approved by the Investigational Review Board (IRB) before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to the sponsor.

8.2 Protocol
Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator's Signature Page. Copies of the IRB approved protocol and informed consents will be provided to the Sponsor.

8.3 Informed Consent
An Informed Consent (IC) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study subject at screening before enrollment into the study. The type and method of study, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by the Investigator and/or the designee. Once the Investigator is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the Informed Consent form. The Investigator and/or Designee will also sign and date the form where indicated. A copy of the IRB approved IC form will also be provided to the Sponsor.

8.4 Protocol and Informed Consent Changes
Changes to the protocol or Informed Consent form(s) will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and IC amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the subject requires the subject's consent to continue in the study.

8.5 Investigational Product Accountability
The Investigational product to be used for this study is the sole property of the Sponsor. All provided products to be used for this study and their receipt, inventory, dispensing, and reconciliation records will be maintained in compliance with Federal Regulations. The study supplies will be dispensed by the Investigator or designee to qualified study subjects according to established procedures. Upon completion or termination of the study the site will be responsible for retaining all partial and unused products under FDA regulations.

8.6 Study Monitoring
All monitoring activities are the responsibility of the study doctor. Monitoring is for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The site will be responsible for internal verification of data throughout the study.

9. Confidentiality of Records

Information about the subject's health taken during this study may be used and given to others by the study coordinators, the medical staff, the respective study center and by the subject's doctors and their other health care providers (together, they are called "providers"). These providers may share health information about the subject with the study coordinator. The study coordinator and the providers may share that information with:

- Researchers participating in this Study laboratories conducting tests for this Study;
- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies;
- Other U.S. and foreign government agencies that watch over quality, safety, and effectiveness of research

10. Delegation of Responsibilities

The Investigator should ensure that all persons assisting with the trial are qualified and are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant trial-related duties.

11. Direct Access to Source Data and Documents

The Investigator must ensure that institutional regulations, the Informed Consent Form, and the HIPAA Authorization clearly permit study-related monitoring, audits, REB review, and regulatory inspections providing direct access to source data and documents.

12. Statistical Hypotheses and Methods of Analyses

12.1 Statistical Hypotheses

The Null Hypothesis: There are no differences in number of actinic keratosis in treatment field after treatment with ingenol mebutate.

Alternative Hypothesis: The number of actinic keratosis in the treatment field is decreased after treatment with ingenol mebutate.

12.2 Statistical Methods

A. Statistical Methods

All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables, frequencies for all categorical variables.

In order to track changes for individual variables across all relevant visits, single-factor Analysis of Variance (ANOVA) tests will be used, while comparisons between two individual visits will be done using two-sample t-tests assuming equal variance.

P-values <0.05 will be considered clinically significant.

B. Efficacy Analyses

i. The primary analyses of efficacy will be based on the change in investigator assessed lesion count from Baseline to Day 59.

ii. Secondary analysis of efficacy variables will include the stratification by percent clearance of all patients, based on the count of lesions remaining at follow-up visits 4, 5, 6, and 7 compared to Baseline, and grade changes in Dyschromia, Erythema (E), Telangiectasia (T), Keratosis, Texture and Rhytides between baseline and follow-up visits 2, 3, 4, 5, 6 and 7.

C. Satisfaction Analyses

Subject satisfaction will be assessed based on surveys taken at follow-up visits 4, 5, 6, and 7.

D. Safety Analyses

The type, severity, duration and frequency of reported adverse events will be tabulated. Adverse events will also be summarized for events that were considered treatment-related.

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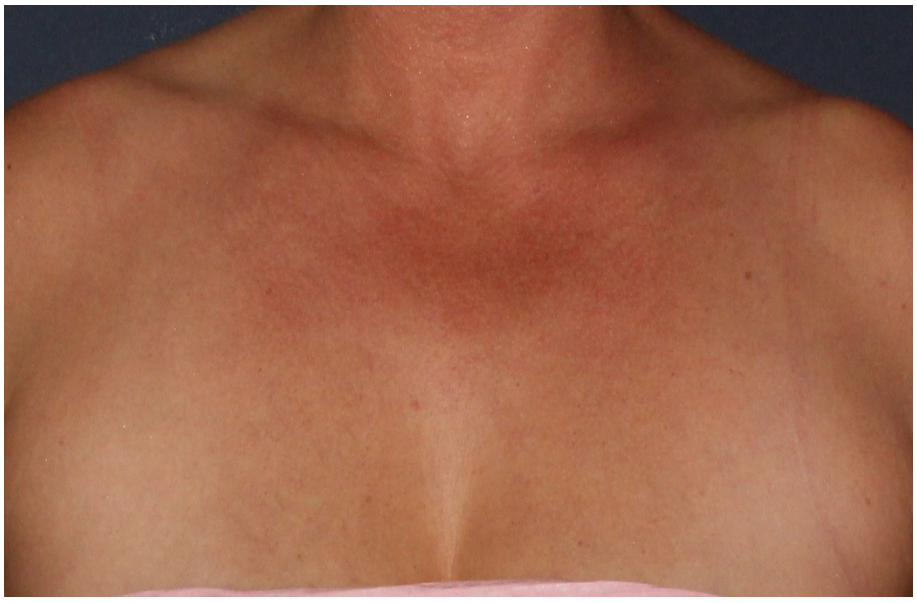
Appendix A

PHOTOS:

Photos will be taken in a standardized fashion:



Prior to taking photos the subjects will be instructed to clean with a baby wipe and dry the entire area of the chest to ensure lotions and/or sunscreens will not interfere with any evaluations.

Subjects will wear a drape wrapped around the lowest point of the chest in front of a dark blue background as shown in the photo. A photo will be taken at every visit (at the screening visit the subject will have photo taken pre-treatment post marking of treatment area).

The camera we will be using is a Canon EOS Rebel T4i, DSLR.

Appendix B

Modified Alexiades-Armenakas Comprehensive Grading Scale of Skin Aging

Grade	Dyschromia	Erythema (E)-Telangiectasia (T)	Keratoses	Texture	Rhytides
0	None	None	None	None	Wrinkles Absent
1	Few (1-3) discrete small (<5mm) lentigenes	Pink E or few localized T	Few	Subtle irregularity	1-6 shallow but visible lines
1.5	Several (4-6) discrete small lentigenes	Pink E or several T in 2 sites	Several	Mild irregularity in few areas	>6shallow but visible lines
2	Multiple (7-10) small lentigenes, few hypopigmented macules	Red E or multiple T localized to 2 sites	Multiple, small	Rough in few, localized sites	1-6 moderately deep lines
2.5	Multiple small and few large lentigenes, several hypopigmented macules	Red E or multiple T localized to 3 sites	Multiple, large	Rough in several localized areas	> 6 moderately deep lines
3	Many (10-20) small and large lentigenes, multiple hypopigmented macules	Violaceous E or many T at multiple sites	Many	Rough in multiple, localized sites	1-6 deep well defined lines
3.5	Numerous (>20) small or multiple large lentigenes, many hypopigmented macules	Violaceous E and numerous T, little uninvolved skin	Numerous	Mostly rough, little uninvolved skin	>6 deep well defined lines
4	Numerous extensive lentigenes, numerous hypopigmented macules	Deep, Violaceous E, numerous T throughout	Numerous, hyperkeratosis present	Rough throughout	Very deep wrinkles with redundant folds

Few 1-3, Several 4-6, Multiple 7-10, Many 10-20, Numerous >20

Appendix C

Patient's Evaluation of Signs of Photoaging							
	Satisfaction of Improvement						
	0 Completely Dissatisfied	**1** Moderately Dissatisfied	**2** Mildly Dissatisfied	**3** Neither Dissatisfied Nor Satisfied	**4** Mildly Satisfied	**5** Moderately Satisfied	**6** Completely Satisfied
Rhytides (Lines/Wrinkles)							
Dyschromia (Changes is skin pigmentation)							
Telangiectasias (Spider Veins)							
Keratosis (Tactile Roughness)							
Erythema (Redness)							
Overall Satisfaction with treatment							

Subject Initial: _____ **Date**: _____/_____/_____

TSQM *(Version 1.4)*

(Subject) Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you used in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last three days, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes

☐0 No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome

☐2 Very Bothersome

☐3 Somewhat Bothersome

☐4 A Little Bothersome

☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your <u>physical</u> health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal

☐2 Quite a Bit

☐3 Somewhat

☐4 Minimally

☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal

☐2 Quite a Bit

☐3 Somewhat

☐4 Minimally

☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal

☐2 Quite a Bit

☐3 Somewhat

☐4 Minimally

☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult

☐2 Very Difficult

☐3 Difficult

☐4 Somewhat Easy

☐5 Easy

☐6 Very Easy

☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult

☐2 Very Difficult

☐3 Difficult

☐4 Somewhat Easy

☐5 Easy

☐6 Very Easy

☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient

☐2 Very Inconvenient

☐3 Inconvenient

☐4 Somewhat Convenient

☐5 Convenient

☐6 Very Convenient

☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident

☐2 A Little Confident

☐3 Somewhat Confident

☐4 Very Confident

☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain

☐2 A Little Certain

☐3 Somewhat Certain

☐4 Very Certain

☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

Subject Initial: _____ **Date**: _____/_____/_____

APPENDIX D

STUDY SUBJECT TAKE HOME INSTRUCTION SHEET

The study regimen you have been given is for you to start the day ***AFTER*** your first office visit. You should apply the PICATO 0.015% gel for the next two (2) days and return to your doctor's office tomorrow ***PRIOR*** to your first in home application!

Instructions for Applying Picato® gel:

1. Open a new tube each time you use Picato® gel
2. Remove cap from tube just before use
3. Squeeze the gel from the tube onto your fingertip. Only use enough gel needed to cover the affected area, as directed by your study doctor
4. Spread the gel evenly over only the skin area to be treated. Allow the treated area to dry for 15 minutes
5. Wash your hands right away after applying Picato® gel
6. Safely throw away (dispose of) the tube after use

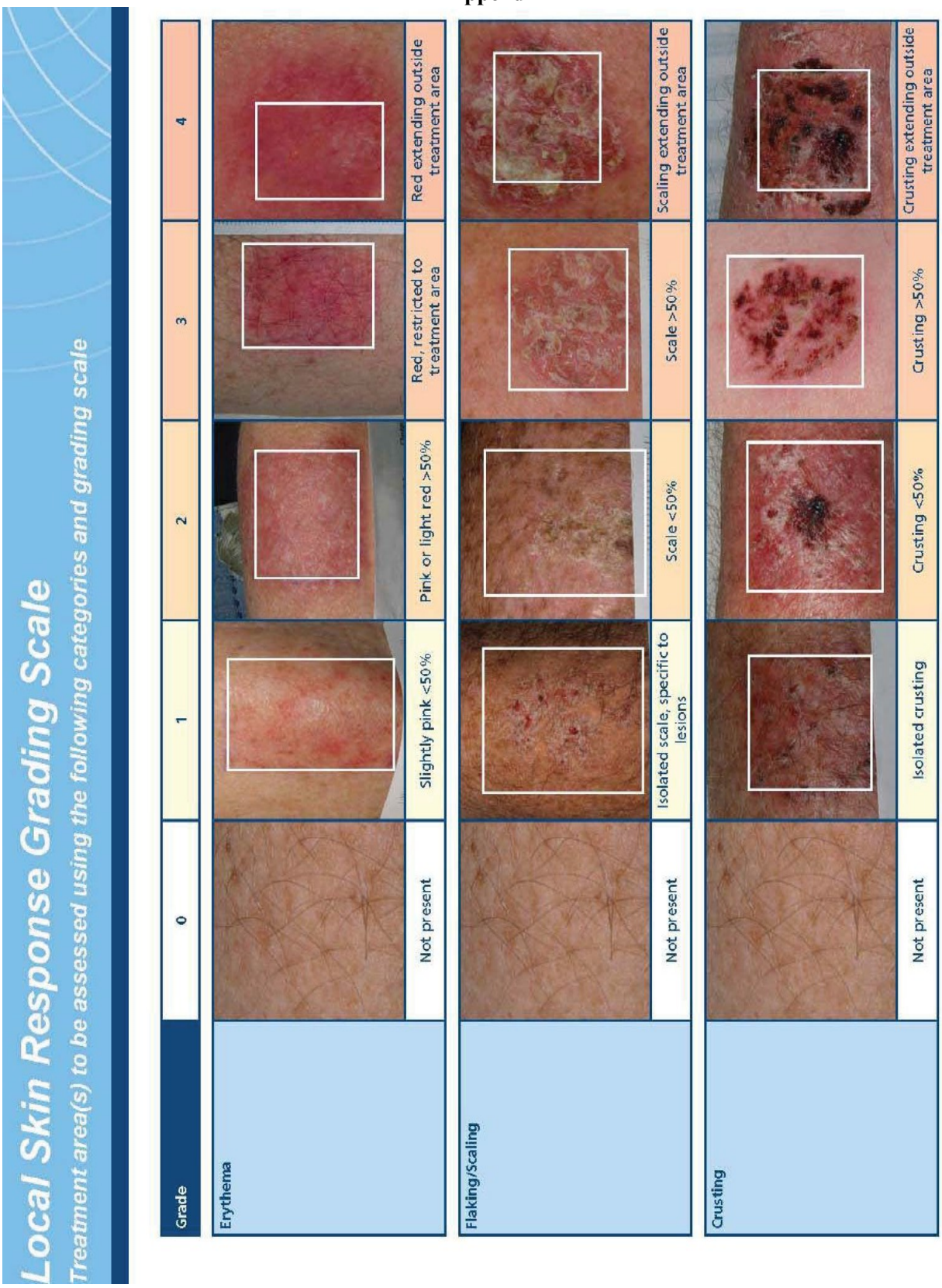
****Repeat the above steps for each day of treatment***

RESTRICTIONS:

- **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
- **DO NOT** cover the treated area with bandages or other dressings after you have applied Picato® gel
- **DO NOT get Picato® gel in 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

If you have any questions about the study, you may contact the doctor's office at: **858-657-1004**

Appendix E


Local Skin Response Grading Scale
Treatment area(s) to be assessed using the following categories and grading scale
Grade
0
1
2
3
4
Erythema
Not present
Slightly pink <50%
Pink or light red >50%
Red, restricted to treatment area
Red extending outside treatment area
Flaking/Scaling
Not present
Isolated scale, specific to lesions
Scale <50%
Scale >50%
Scaling extending outside treatment area
Crusting
Not present
Isolated crusting
Crusting <50%
Crusting >50%
Crusting extending outside treatment area

Local Skin Response Grading Scale

Treatment area(s) to be assessed using the following categories and grading scale

Grade	0	1	2	3	4
Swelling	Not present	Slight, lesion specific oedema	Palpable oedema extending beyond individual lesions	Confluent and/or visible oedema	Marked swelling extending outside treatment area
Vesiculation/ Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles <50%	Transudate or pustules, with or without vesicles >50%	Transudate or pustules, with or without vesides extending outside treatment area
Erosion/ Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

APPENDIX F

RESPONSIBILITIES OF THE INVESTIGATOR

1. ADHERENCE TO THE STUDY PROTOCOL

The Investigator must ensure adherence to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: "Guideline for Good Clinical Practice." Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

2. DATA HANDLING AND RECORD KEEPING

The Investigator must ensure that proper source documentation for all study activities are diligently maintained and securely kept. The Investigator will sign the source documents for completeness, accuracy and integrity of the data collected. The Investigator will maintain reliable study Medication/Device dispensing/dosing records and will store study supplies in a secure, locked location. In addition, the Investigator will ensure that all study-related source documentation will be maintained for a period of two years after the conclusion of the study.

3. Regulatory Obligations

a. Institutional Review Board

The study protocol, informed consent forms (all versions), and any specific advertising will be submitted to and approved by the Investigational Review Board (IRB) before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to the sponsor.

9 Protocol

Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator's Signature Page. Copies of the IRB approved protocol and informed consents will be provided to the Sponsor.

10 Informed Consent

An Informed Consent (IC) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study subject at screening before enrollment into the study. The type and method of study, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by the Investigator and/or the designee. Once the Investigator is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the Informed Consent form. The Investigator and/or Designee will also sign and date the form where indicated. A copy of the IRB approved IC form will also be provided to the Sponsor.

11 Protocol and Informed Consent Changes

Changes to the protocol or Informed Consent form(s) will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and IC amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the subject requires the subject's consent to continue in the study.

12 Investigational Product Accountability

The Investigational product to be used for this study is the sole property of the Sponsor. All provided products to be used for this study and their receipt, inventory, dispensing, and reconciliation records will be maintained in compliance with Federal Regulations. The study supplies will be dispensed by the Investigator or designee to qualified study subjects according to established procedures. Upon completion or termination of the study the site will be responsible for retaining all partial and unused products under FDA regulations.

13 Study Monitoring

All monitoring activities are the responsibility of the study doctor. Monitoring is for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The site will be responsible for internal verification of data throughout the study.

4. Confidentiality of Records

Information about the subject's health taken during this study may be used and given to others by the study coordinators, the medical staff, the respective study center and by the subject's doctors and their other health care providers (together, they are called "providers"). These providers may share health information about the subject with the study coordinator. The study coordinator and the providers may share that information with:

- researchers participating in this Study laboratories conducting tests for this Study;
- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies;
- Other U.S. and foreign government agencies that watch over quality, safety, and effectiveness of research

5. DELEGATION OF INVESTIGATOR RESPONSIBILITIES (ADHERENCE TO THE STUDY PROTOCOL)

The Investigator should ensure that all persons assisting with the trial are qualified and are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant trial-related duties.

6. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must ensure that institutional regulations, the Informed Consent Form, and the HIPAA Authorization clearly permit study-related monitoring, audits, REB review, and regulatory inspections providing direct access to source data and do

APPENDIX G

IMPORTANT SAFETY INFORMATION FOR

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
----------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)
 Actinic keratosis on the face and scalp: Apply Picato® gel, 0.015% to the affected area once daily for 3 consecutive days. (2)
 Actinic keratosis on the trunk and 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----------
None. (4)
----------WARNINGS AND PRECAUTIONS----------
Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure. Avoid contact with 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. (5.2)
----------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: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 **INDICATIONS AND USAGE**
2 **DOSAGE AND ADMINISTRATION**
3 **DOSAGE FORMS AND STRENGTHS**
4 **CONTRAINDICATIONS**
5 **WARNINGS AND PRECAUTIONS**
5.1 Eye Exposure
5.2 Local Skin Reactions
6 **ADVERSE REACTIONS**
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8 **USE IN SPECIFIC POPULATIONS**
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*Sections or subsections omitted from the Full Prescribing Information are not listed.

Reference ID: 3075879

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.

For the treatment of actinic keratosis on the face and 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 and 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

None.

5 WARNINGS AND PRECAUTIONS

5.1 Eye Exposure

Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure *[see Adverse Reactions (6)]*. Patients should wash hands well after applying Picato® gel, and avoid transfer of the drug to the periocular area during and after application [*see Patient Counseling Information (17)*]. If accidental exposure occurs, the area should be flushed with water and the patient should seek medical care as soon as possible *[see Adverse Reactions (6)]*.

5.2 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

Reference ID: 3075879

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)

SKIN REACTIONS	FACE AND SCALP (N=545)		PICATO® GEL, 0.015% ONCE DAILY FOR 3 DAYS	
	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%)

[a]Mild (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)

SKIN REACTIONS	TRUNK AND EXTREMITIES (N=457)		PICATO® GEL, 0.05% ONCE DAILY FOR 2 DAYS	
	ANY GRADEA > 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%)

[a]Mild (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 ≥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 ≥ 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 ≥ 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® 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.

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.

Reference ID: 3075879

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

Or (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1*H* 2,8a-methanocyclopenta[*a*]cyclopropa[*e*]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. Reference ID: 3075879

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®-treated subjects were Caucasian. Reference ID: 3075879

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.

Table 5 Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in 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.
Table 6 Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by 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®-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 Reference ID: 3075879 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.

Table 7 Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in Each Trial

	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.

Table 8 Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Trial

	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 %)

[a]Other 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

Reference ID: 3075879

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

17 PATIENT COUNSELING INFORMATION

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

Picato® gel should be used as directed by a physician.

Picato® gel is for external use only. Advise patients to avoid contact with the eyes. Inform patients that treatment with Picato® gel may lead to local skin reactions [*see Warnings and Precautions (5)*].

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.

 keep out of the reach of children.

Reference ID: 3075879