CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

APPROVAL LETTER

NDA 20-965

Guidelines, Incorporated
Attention: Mr. Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance
10320 USA Today Way
Miramar, Florida 33025

Dear Mr. Swetland:

Please refer to your new drug application (NDA) dated June 29, 1998, received July 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, for use in photodynamic therapy with blue light irradiation using the BLU-U™ Illuminator.

We acknowledge receipt of your submissions dated June 21, July 7 and 28, October 1, 8 and 11, November 11, and December 2 and 3, 1999 (facsimiles). Your submission of October 1, 1999, constituted a complete response to our June 27, 1999, action letter.

This new drug application provides for the use of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, when used with blue light irradiation using the BLU-U™ Illuminator for the photodynamic therapy of actinic keratoses of the face and scalp.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, carton and applicator labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission s' ould be designated "FPL for approved NDA 20-965." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated October 1, and December 2, 1999. These commitments, along with any completion dates agreed upon, are listed below:

1. A commitment to characterize the potential for dermal allergenicity of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, within 24 months of approval.

2. A commitment to characterize the safety and efficacy of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, plus blue light photodynamic therapy to assess the long-term recurrence rate of actinic keratosis lesions over a 12-month follow-up period. As part of this study, the histopathology of treated actinic keratosis lesions (including lesions that recur in long-term follow-up) should be characterized. Patients with Fitzpatrick skin types IV-VI should be included in this study. This study would be completed within 4 years of approval.

3. A commitment to re-evaluate the drug substance and drug product specification limits for [ ] once adequate data are available.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely,

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 28, 1999. Number of Pages (including cover sheet) 29
TO: Mr. Samuel Swetland, Vice President, Regulatory Affairs and Compliance
COMPANY: Guidelines, Inc.
NUMBER: 954-432-9015

MESSAGE: **RE: NDA 20-965**

LEVULAN KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20%

Please find approvable letter for this NDA with revised draft labeling.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

cc: NDA 20-965
HFD-540/Div Files

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-965

JUN 27 1999

Guidelines, Incorporated
Attention: Mr. Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance
10320 USA Today Way
Miramar, Florida 33025

Dear Mr. Swetland:

Please refer to your new drug application (NDA) dated June 29, 1998, received July 1, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, for use in photodynamic therapy with blue light irradiation using the BLU-U™ Illuminator.

We acknowledge receipt of your submissions dated August 18 and 20, September 30, October 14, November 4, and December 1, 1998; February 17 and 26, March 11, 15 and 31, April 16, 26 and 30 (two), and June 2, 1999.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. During a recent pre-approval inspection, your manufacturer of 5-aminolevulinic acid hydrochloride was found to be non-compliant with our current Good Manufacturing Practices regulations. Satisfactory inspections will be required for all manufacturing and testing facilities before this application may be approved.

2. Submit draft labeling for the drug product revised as recommended in the enclosed revised draft labeling (text for the package insert, carton and applicator labels). Should additional information relating to the safety or effectiveness of this drug become available, revision of the labeling may be required.

Although not approvability issues, you should address the following informational needs.

Clinical:

a. Characterization of the potential for dermal irritancy with LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%.

b. Characterization of the potential for dermal allergenicity with LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%.

c. Characterization of the safety and efficacy of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, plus blue light photodynamic therapy when used in the manner described in the proposed labeling in different skin types. At least 70 patients should be enrolled. The investigators should be qualified health care professionals. To assess the safety profile in patients with Fitzpatrick skin types IV-VI, at least 30 of the enrolled patients should have Fitzpatrick skin types IV-VI. The safety evaluation should include laboratory evaluations of hematocrit and levels of urinary aminolevulinic acid, before and after treatment. Patients should be seen in follow-up at one year after treatment to assess the long term recurrence rate of actinic keratoses that have resolved after treatment with LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, plus blue light photodynamic therapy.

d. Characterization of the safety and efficacy of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, plus blue light photodynamic therapy for the treatment of actinic keratoses of the back and arms.

Chemistry:

a. In order to conform with the conventions set forth in the ICH Q3A guidance document "Impurities in New Drug Substances", the drug substance specification should be revised as and The limit for should be set at "less than or equal to

b. In order to conform with the conventions set forth in the ICH Q3B guidance document "Impurities in New Drug Products", the drug product regulatory specification should be revised as and The limit for should be set at "less than or equal to

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time

of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely,

/S/

Robert J. DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

25 Page(s) Redacted

Draft

Labeling