DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

D. Geoffrey Shulman, MD, FRCPC
Chairman of the Board and Chief Executive Officer
DUSA Pharmaceuticals, Inc.
25 Upton Drive
Wilmington, MA 01887

RE: NDA # 20-965
Levulan® Kerastick® (aminolevulinic acid HCl) for Topical Solution, 20%
MACMIS ID # 15170

WARNING LETTER

Dear Dr. Shulman:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed an advertisement (MKT-1330 Rev C) for Levulan Kerastick (aminolevulinic acid HCl) for Topical Solution, 20% (Levulan Kerastick) submitted by DUSA Pharmaceuticals, Inc. (DUSA) under cover of Form FDA 2253. The advertisement is false or misleading because it presents efficacy claims for Levulan Kerastick, but omits and minimizes the risks associated with the use of the drug, broadens the indication, and overstates the efficacy of the drug. Therefore, the advertisement misbrands Levulan Kerastick in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(n) and 321(n), and FDA's implementing regulations. *See* 21 CFR 202.1(e)(5); (e)(6)(i). This advertisement raises significant public health and safety concerns because it suggests that Levulan Kerastick is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the product labeling (PI):

> The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1 or 2, see table 2 for definition**)** of the face or scalp.

According to table 2, Grade 1 lesions are defined as slightly palpable actinic keratoses that are better felt than seen and Grade 2 lesions are moderately thick actinic keratoses that are easily seen and felt.

The PI also includes the following risk information (in pertinent part):

CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

WARNINGS

The LEVULAN KERASTICK for Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

PRECAUTIONS

General*:*
During the time period between the application of LEVULAN KERASTICK Topical Solution and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

Drug Interactions:
There have been no formal studies of the interaction of LEVULAN KERASTICK for Topical Solution with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with the LEVULAN KERASTICK for Topical Solution.

Finally**,** the Adverse Reactions section of the PI states:

The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution

> Photodynamic Therapy for actinic keratoses treatment….. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment….The most common changes in lesion appearance after LEVULAN KERASTICK Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy.

The most common adverse events associated with Levulan Kerastick were: Scaling/Crusting (71% face and 64% scalp of mild/moderate severity), Hypo/hyper-pigmentation (22% face and 36% scalp), and Itching (25% face and 14% scalp of mild/moderate severity).

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The advertisement is misleading because it presents claims for Levulan Kerastick but fails to present any risk information.

The advertisement includes the following claims:

- "**Treats AKs *without* weeks of red, raw skin**"
- "**94%** rated ***cosmetic response*** as good to excellent"
- "This is why 4 out of 5 patients prefer **Levulan** to previous 5-FU treatments"

(original emphasis)

However, the advertisement entirely omits risk information for Levulan Kerastick, including the most serious and frequently occurring risks associated with the drug. The statement, "See attached full prescribing information for additional details" in very small type at the lower left-hand corner of the advertisement does not mitigate this misleading presentation. As a result, the advertisement misleadingly suggests that Levulan Kerastick is safer than has been demonstrated by substantial evidence or substantial clinical experience.

In addition to omitting the risks associated with Levulan Kerastick, the advertisement also presents claims that minimize risks associated with Levulan Kerastick use. Specifically, the advertisement claims, "**Treats AKs *without* weeks of red, raw skin**. Instead, skin response usually subsides within a week of treatment…." This claim is inconsistent with the Adverse Reactions section of the PI, which states, "Both erythema and edema resolved to baseline or improved by **4 weeks** after therapy." (emphasis added.)

Broadening of Indication

The advertisement is also misleading because it suggests that Levulan Kerastick is safe and effective for use in a broader patient population or under broader conditions than has been demonstrated by substantial evidence or substantial clinical experience. The advertisement contains representations that

promote the use of Levulan Kerastick to treat the broad population of patients with "AK." For example, the advertisement claims that Levulan photodynamic therapy "Treats AKs without weeks of red, raw skin." The PI identifies limitations to the use of Levulan Kerastick for actinic keratoses. Specifically, according to the Indications and Usage section, "The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1 or 2, see table 2 for definition) of the face or scalp." According to table 2, Grade 1 lesions are defined as slightly palpable actinic keratoses that are better felt than seen and Grade 2 lesions are moderately thick actinic keratoses that are easily seen and felt. Levulan Kerastick was not studied, and therefore is not indicated for Grade 3 lesions that are defined as very thick and/or hyperkeratotic actinic keratoses. In addition, Levulan Kerastick is only indicated for the face or scalp. By failing to identify the limitations to its indication, this claim implies that Levulan Kerastick is useful for the treatment of all patients with actinic keratoses when this is not the case.

Overstatement of Efficacy

The advertisement includes the claim, "This is why 4 out of 5 patients prefer **Levulan** to previous 5-FU treatments." This claim is misleading for the following reasons. The reference cited to support this claim is a study conducted in 27 patients who were asked one question about the acceptability of Levulan Kerastick therapy on a 3-Point Comparability Scale comparing Levulan Kerastick to patients' other prior therapies for actinic keratosis. This is an open-label study that does not directly compare Levulan Kerastick with its competitors. Accordingly, there are many reasons for a stated preference for the more recent treatment other than actual superiority. For example, patients may have preferred Levulan Kerastick because they were a subgroup of people who took 5-FU without good response. They may have also stated a preference for Levulan Kerastick because they recalled the more recent treatment better, because they liked the investigator, because the treatment was free, or for a variety of other reasons that are not actually related to the treatment. Additionally, patient "preference" encompasses multiple aspects of patient experiences with the drugs such as efficacy, side effects, dosing, and ease of administration and therefore cannot be adequately measured by one single item. Such a claim should be based on evidence from an adequate and well-controlled study or studies using validated and well-developed instruments to demonstrate that patients indeed prefer Levulan Kerastick to 5-FU treatments.

Conclusion and Requested Action

For the reasons discussed above, your advertisement misbrands Levulan Kerastick in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(n) and 321(n), and FDA's implementing regulations. *See* 21 CFR 202.1(e)(5); (e)(6)(i).

DDMAC requests that DUSA immediately cease the dissemination of violative promotional materials for Levulan Kerastick such as those described above. Please submit a written response to this letter on or before May 4, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Levulan Kerastick the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research,

Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to the MACMIS #15170 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Levulan Kerastick comply with each applicable requirement of the Act and FDA implementing regulations. Furthermore, claims regarding the use of the BLU-U Blue Light Photodynamic Therapy Illuminator device alone were not evaluated by DDMAC. It is also your responsibility to ensure that promotional claims regarding the device comply with the applicable requirements of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

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