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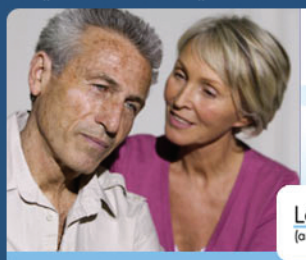

Levulan® Kerastick®
(aminolevulinic acid HCl) for Topical Solution, 20%

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Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

For Topical Use Only • Not for Ophthalmic Use

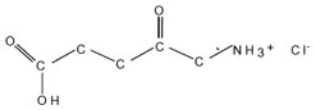
DESCRIPTION

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

hydrochloride salt of aminolevulinic acid (ALA), an endogenous 5-carbon aminoketone.

Aminolevulinic acid HCl (ALA HCl) is a white to off-white, odorless crystalline solid that is very soluble in water, slightly soluble in methanol and ethanol, and practically insoluble in chloroform, hexane and mineral oil.

The chemical name for ALA HCl is 5-amino-4-oxopentanoic acid hydrochloride (MW = 167.59). The structural formula is represented below:



The LEVULAN KERASTICK for Topical Solution applicator is a two component system consisting of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle comprising alcohol USP (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of ALA HCl as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. The 20% topical solution is prepared just prior to the time of use by breaking the ampules and mixing the contents by shaking the LEVULAN KERASTICK applicator. The term "ALA HCl" refers to unformulated active ingredient, "LEVULAN KERASTICK for Topical Solution" refers to the drug product in its unmixed state, "LEVULAN KERASTICK Topical Solution" refers to the mixed drug product (in the applicator tube or after application), and "LEVULAN KERASTICK" refers to the applicator only.

CLINICAL PHARMACOLOGY

Pharmacology: The metabolism of aminolevulinic acid (ALA) is the first step in the biochemical pathway resulting in heme synthesis. Aminolevulinic acid is not a photosensitizer, but rather a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. The synthesis of ALA is normally tightly controlled by feedback inhibition of the enzyme, ALA synthetase, presumably by intracellular heme levels. ALA, when provided to the cell, bypasses this control point and results in the accumulation of PpIX, which is converted into heme by ferrochelatase through the addition of iron to the PpIX nucleus.

According to the presumed mechanism of action, photosensitization following application of LEVULAN KERASTICK Topical Solution occurs through the metabolic conversion of ALA to PpIX, which accumulates in the skin to which LEVULAN Topical Solution has been applied. When exposed to light of appropriate wavelength and energy, the accumulated PpIX produces a photodynamic reaction, a cytotoxic process dependent upon the simultaneous presence of light and oxygen. The absorption of light results in an excited state of the porphyrin molecule, and subsequent spin transfer from PpIX to molecular oxygen generates singlet oxygen, which can further react to form superoxide and hydroxyl radicals. Photosensitization of actinic (solar) keratosis lesions using the LEVULAN KERASTICK for Topical Solution, plus illumination with the BLU-U® Blue Light Photodynamic Therapy Illuminator (BLU-U), is the basis for LEVULAN photodynamic therapy (PDT).

Pharmacokinetics: In a human pharmacokinetic study (N=6) using a 128 mg dose of sterile intravenous ALA HCl and oral ALA HCl (equivalent to 100 mg ALA) in which plasma ALA and PpIX were measured, the mean half-life of ALA was 0.70 ± 0.18 h after the oral dose and 0.83 ± 0.05 h after the intravenous dose. The oral bioavailability of ALA was 50-60% with a mean Cmax of 4.65 ± 0.94 µg/mL. PpIX concentrations were low and were detectable only in 42% of the plasma samples. PpIX concentrations in plasma were quite low relative to ALA plasma concentrations, and were below the level of detection (10 ng/mL) after 10 to 12 hours.

ALA does not exhibit fluorescence, while PpIX has a high fluorescence yield. Time-dependent changes in surface fluorescence have been used to determine PpIX accumulation and clearance in actinic keratosis lesions and perilesional skin after application of LEVULAN KERASTICK Topical Solution in 12 patients. Peak fluorescence intensity was reached in 11 ± 1 h in actinic keratoses and 12 ± 1 h in perilesional skin. The mean clearance half-life of fluorescence for lesions was 30 ± 10 h and 28 ± 6 h for perilesional skin. The fluorescence in perilesional skin was similar to that in actinic keratoses. Therefore, LEVULAN

KERASTICK Topical Solution should only be applied to the affected skin.

Clinical Studies: LEVULAN KERASTICK for Topical Solution, 20%, plus blue light at 6-10.9 J/cm2, has been used to treat actinic keratoses in 232 patients in six clinical trials. Phase 3 studies were two, identically designed, multicenter, two-arm studies using LEVULAN KERASTICK for Topical Solution applicators plus illumination from the BLU-U for 1000 seconds (16 min 40 sec) for a nominal exposure of 10 J/cm2. Patients were excluded from these studies who had a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, photodermatosis, or inherited or acquired coagulation defects. A minimum of 4 and a maximum of 15 clinically typical, discrete, (Grade 1 or 2, see table 2 for definition), target actinic keratosis lesions were identified. Target lesions on the face or on the scalp, but not in both locations in the same patient, received treatment. The patients were randomized to receive treatment either with the LEVULAN KERASTICK Topical Solution plus BLU-U or vehicle plus BLU-U. Patients were randomized at a 3 to 1 LEVULAN to vehicle ratio. A total of 243 patients were enrolled in two Phase 3 studies (ALA-018, ALA-019). Lesions were designated as cleared (complete response) if the lesion had completely cleared and adherent scaling plaques of actinic keratoses were no longer evident on the surface of the treated skin when palpated. The percentage of patients in whom 75% or more of treated lesions were cleared, and the percentage of patients in whom 100% of treated lesions were cleared (Complete Responders), for each study at 8 weeks after treatment are shown in Table 1.

TABLE 1 Patient Responses at Week 8

	ALA-018		**ALA-019**	
	LEVULAN	Vehicle	LEVULAN	Vehicle
	Patients with > 75% of AK Lesions Cleared			
Total No. Patients	68/87 (78%)	6/29 (21%)	71/93 (76%)	8/32 (25%)
Patients with Face Lesions	57/71 (80%)	2/21 (10%)	57/67 (85%)	7/19 (37%)
Patients with Scalp Lesions	11/16 (69%)	4/8 (50%)	14/26 (54%)	1/13 (8%)
	Complete Responders			
Total No. Patients	60/87 (69%)	4/29 (14%)	59/93 (63%)	4/32 (13%)
Patients with Face Lesions	49/71 (69%)	2/21 (10%)	47/67 (70%)	4/19 (21%)
Patients with Scalp Lesions	11/16 (69%)	2/8 (25%)	12/26 (46%)	0/13 (0%)

Because clinical studies ALA-018 and ALA-019 had identical protocols, the combined results from the two trials are shown in the following tables. For actinic keratoses with a variety of thicknesses (excluding very thick, Grade 3 actinic keratoses which were not studied in the phase 3 trials), LEVULAN KERASTICK Topical Solution plus BLU-U is more effective than vehicle plus BLU-U, but as shown in Table 2, the percentage of lesions with complete responses at 8 weeks after treatment with LEVULAN KERASTICK Topical Solution plus blue light illumination was lower for those lesions that were thicker at baseline. Efficacy of LEVULAN KERASTICK Topical Solution plus BLU-U on higher grade lesions was not studied in the Phase 3 clinical efficacy trials.

TABLE 2 Lesions Complete Responses at Week 8 for Different Lesion Grades

	LEVULAN	Vehicle
Lesion Grade 1 (Slightly palpable actinic keratoses: better felt than seen)	666/756 (88%)	122/302 (40%)
Lesion Grade 2 (Moderately thick actinic keratoses: easily seen and felt)	495/632 (78%)	52/199 (26%)
Lesion Grade 3 (Very Thick and/or hyperkeratotic actinic keratoses)	0	0

Those patients who were not Complete Responders at week 8 had retreatment of the persistent target lesions at week 8. Among the patients undergoing retreatment, efficacy results seen at 12 weeks after the initial treatment, i.e., at 4 weeks after the second treatment, are shown in Table 3.

TABLE 3 Complete Responders at Week 12, among Patients Receiving Two Treatments

	LEVULAN	Vehicle
Total No. Patients	24/56 (43%)	2/49 (4%)
Patients with Face Lesions	21/40 (53%)	2/31 (6%)
Patients with Scalp Lesions	3/16 (19%)	0/18 (0%)

The efficacy results seen at 12 weeks after treatment, which include the results at 12 weeks for those patients who received a single treatment as well as the results at 12 weeks for those patients who received a second treatment at week 8, are shown in Table 4.

TABLE 4 Patient Responses at Week 12, among Patients who Received One or Two Treatments

	LEVULAN	Vehicle
	Patients with > 75% of AK Lesions Cleared	
Total No. Patients	158/180 (88%)	12/61 (20%)
Patients with Face Lesions	127/138 (92%)	8/40 (20%)
Patients with Scalp Lesions	31/42 (74%)	4/21 (19%)
	Complete Responders	
Total No. Patients	129/180 (72%)	7/61 (11%)
Patients with Face Lesions	108/138 (78%)	5/40 (13%)
Patients with Scalp Lesions	21/42 (50%)	2/21 (10%)

Among Complete Responders at week 8, 93% (in study ALA-018) and 83% (in study ALA-019) maintained complete response at week 12. Among patients with scalp lesions, the percentage of patients with 100% of AK lesions having complete response declined from week 8 (55%) to week 12 (50%), because there were more patients with scalp lesions with 100% of AK lesions cleared at week 8 who had a recurrence of a lesion by week 12 than there were patients with scalp lesions who had retreatment of persistent lesions at week 8 and who then achieved 100% of AK lesions cleared by week 12. Patients did not receive follow-up past 12 weeks after the initial treatment.

Patient outcomes recorded in the two Phase 3 trials are depicted in the following flowchart, in which

Complete Responders are designated clear. Seven patients in the active treatment arm and three patients in the vehicle treatment arm withdrew or were lost to follow-up, and their outcomes are not included in the flowchart. Three patients in the active treatment arm were treated at baseline but did not return for evaluation until week 12. One patient in the active treatment arm and two in the vehicle treatment arm who were not clear at week 8 did not receive retreatment.

INDICATIONS AND USAGE

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.

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.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK for Topical Solution should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

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

Information for Patients:

LEVULAN Photodynamic Therapy for Actinic Keratoses.

The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK Topical Solution to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear lightprotective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion

changes are temporary and should completely resolve by 4 weeks after treatment.

Photosensitivity

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitive actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

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.

Carcinogenesis, Mutagenesis, Impairment to Fertility: No carcinogenicity testing has been carried out using ALA. No evidence of mutagenic effects was seen in four studies conducted with ALA to evaluate this potential. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK± mouse lymphoma forward mutation assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these in vitro studies. In the in vivo mouse micronucleus assay, ALA was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA exposure with PpIX formation. Other studies have documented oxidative DNA damage in vivo and in vitro as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

Pregnancy Category C: Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLUU treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the 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 majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

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. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

Other Localized Cutaneous Adverse Experiences: Table 5 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

TABLE 5 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/ Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%

Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/ Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/ hyperpigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0%

Adverse Experiences Reported by Body System: In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose: LEVULAN KERASTICK Topical Solution overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose: There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

DOSAGE AND ADMINISTRATION

LEVULAN KERASTICK for Topical Solution 20% is intended for direct application to individual lesions diagnosed as actinic keratoses and not to perilesional skin. This product is not intended for application by patients or unqualified medical personnel. Application should involve either scalp or face lesions, but not both simultaneously. The recommended treatment frequency is: one application of the LEVULAN KERASTICK Topical Solution and one dose of illumination per treatment site per 8-week treatment session. Each individual LEVULAN KERASTICK should be used for only one patient. Photodynamic therapy for actinic keratoses with LEVULAN KERASTICK for Topical Solution is a two stage process involving a) application of the product to the target lesions with LEVULAN KERASTICK Topical Solution, followed 14 to 18 hours later by b) illumination with blue light using the BLU-U Blue Light Photodynamic Therapy Illuminator. The second visit, for illumination, must take place in the 14 18 hour window following application. Patients in clinical trials usually received application in the late afternoon, with illumination the following morning.

TABLE 6 Schedule for LEVULAN and Blue Light Administration

LEVULAN KERASTICK Topical Solution Application	Time Window for Blue Light Illumination
6 am	8 pm to Midnight
7 am	9 pm to 1 am
8 am	10 pm to 2 am
9 am	11 pm to 3 am
10 am	Midnight to 4 am
11 am	1 am to 5 am
12 pm	2 am to 6 am
1 pm	3 am to 7 am
2 pm	4 am to 8 am
3 pm	5 am to 9 am
4 pm	6 am to 10 am
5 pm	7 am to 11 am
6 pm	8 am to Noon
7 pm	9 am to 1 pm
8 pm	10 am to 2 pm
9 pm	11 am to 3 pm
10 pm	Noon to 4 pm

Treated lesions that have not completely resolved after 8 weeks may be treated a second time with LEVULAN KERASTICK for Topical Solution Photodynamic Therapy. Patients did not receive follow-up past 12 weeks after the initial treatment, so the incidence of recurrence of treated lesions past 12 weeks and the role of further treatment is not known.

Step A - LEVULAN KERASTICK for Topical Solution Application: Actinic keratoses targeted for treatment should be clean and dry prior to application of LEVULAN KERASTICK for Topical Solution.

Preparation:

The LEVULAN KERASTICK Topical Solution should be prepared as follows:

1. Hold the LEVULAN KERASTICK so that the applicator cap is pointing up.

2. Crush the bottom ampule containing the solution vehicle by applying finger pressure to Position A on the cardboard sleeve.

3. Crush the top ampule containing the ALA HCl powder by applying finger pressure to Position B on the cardboard sleeve. NOTE: To ensure both ampules are crushed continue crushing the applicator downward, applying finger pressure to Position A.

4. Holding the LEVULAN KERASTICK between the thumb and forefinger, point the applicator cap away from the face, shake the LEVULAN KERASTICK gently for at least 3 minutes to completely dissolve the drug powder in the solution vehicle. Do not press on the end cap while shaking.

LEVULAN KERASTICK Preparation: Following solution admixture, remove the cap from the LEVULAN KERASTICK. The dry applicator tip should be dabbed on a gauze pad until uniformly wet with solution.

Application:

Apply the solution directly to the target lesions by dabbing gently with the wet applicator tip. Enough solution should be applied to uniformly wet the lesion surface, including the edges without excess running or dripping. The effect of LEVULAN KERASTICK Topical Solution on ocular tissues is unknown. LEVULAN KERASTICK Topical Solution should not be applied to the periorbital area or allowed to contact ocular or mucosal surfaces. Once the initial application has dried, apply again in the same manner. The LEVULAN KERASTICK Topical Solution must be used immediately following preparation (dissolution) due to the instability of the activated product. If the solution application is not completed within 2 hours of activation, the applicator should be discarded and a new LEVULAN KERASTICK for Topical Solution used.

Photosensitization of the treated lesions will take place over the next 14-18 hours. The actinic keratoses should not be washed during this time. The patient should be advised to wear a wide brimmed hat or other protective apparel to shade the treated actinic keratosis lesions from sunlight or other bright light sources until BLU-U treatment. The patient should be advised to reduce light exposure if the sensations of stinging and/or burning are experienced.

If for any reason the patient cannot be given BLU-U treatment during the prescribed time after LEVULAN KERASTICK Topical Solution application, he or she may nonetheless experience sensations of stinging and/or burning if the photosensitized actinic keratoses are exposed to sunlight or prolonged or intense light at that time. The patient should be advised to wear a wide-brimmed hat or other protective apparel to shade the treated actinic keratosis lesions from sunlight or other bright light sources until at least 40 hours after the application of LEVULAN KERASTICK Topical Solution. The patient should be advised to reduce light exposure if the sensations of stinging and/or burning are experienced.

Step B - Administration of BLU-U Treatment 14 to 18 hours after application of LEVULAN

KERASTICK Topical Solution: At the visit for light illumination, the actinic keratoses to be treated should be gently rinsed with water and patted dry. Photoactivation of actinic keratoses treated with LEVULAN KERASTICK Topical Solution is accomplished with BLU-U illumination from the BLU-U Blue Light Photodynamic Therapy Illuminator. A 1000 second (16 minutes 40 seconds) exposure is required to provide a 10 J/cm2 light dose. During light treatment, both patients and medical personnel should be provided with blue blocking protective eyewear, as specified In the BLU-U Operating Instructions, to minimize ocular exposure. Please refer to the BLU-U Operating Instructions for further information on conducting the light treatment. Patients should be advised that transient stinging and/or burning at the target lesion sites occurs during the period of light exposure.

If blue light treatment with the BLU-U Blue Light Photodynamic Therapy Illuminator is interrupted or stopped for any reason, it should not be restarted and the patient should be advised to protect the treated lesions from exposure to sunlight or prolonged or intense light for at least 40 hours after application of the LEVULAN KERASTICK Topical Solution from the first visit.

For patients with facial lesions:

1.The BLU-U Blue Light Photodynamic Therapy Illuminator is positioned so that the base is slightly above the patient's shoulder, parallel to the patient's face.

2. The BLU-U is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the BLU-U surface:

a) The patient's nose should be no closer than 2" from the surface;

b) The patient's forehead and cheeks should be no further than 4" from the surface;

c) The sides of the patient's face and the patient's ears should be no closer than 2" from the BLU-U surface.

A Chin Rest, available from DUSA Pharmaceuticals, Inc., may be used to provide support for the patient's head during treatment.

For patients with scalp lesions:

1. The knobs on either side of the BLU-U are loosened and the BLU-U is rotated to a horizontal position.

2. The BLU-U is positioned around the patient's head so the entire surface area to be treated lies between

2" and 4" from the BLU-U surface:

a) The patient's scalp should be no closer than 2" from the surface;

b) The patient's scalp should be no further than 4" from the surface;

c) The sides of the patient's face and the patient's ears should be no closer than 2" from the BLU-U surface.

A Chin Rest, available from DUSA Pharmaceuticals, Inc., may be used to provide support for the patient's head during treatment.

LEVULAN KERASTICK for Topical Solution is not intended for use with any device other than the BLU-U Blue Light Photodynamic Therapy Illuminator. Use of LEVULAN KERASTICK for Topical Solution without subsequent BLU-U illumination is not recommended.

HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a single-unit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle. The other ampule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

Product Package	NDC number
Individual LEVULAN KERASTICK for Topical Solution, 20%	67308-101-01
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20%	67308-101-06

Storage Conditions: Store between 20° - 25 °C (68° - 77 °F); excursions permitted to 15°- 30 °C (59° - 86 °F) [See USP Controlled Room Temperature].The LEVULAN KERASTICK for Topical Solution should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution used, if needed.

Rx

LEVULAN®, KERASTICK®, BLU-U®, DUSA Pharmaceuticals, Inc.® and DUSA® are registered trademarks of DUSA Pharmaceuticals, Inc.®

US Patents: 5,079,262, 5,211,938, 5,422,093, 5,954,703, 6,710,066

Manufactured for:

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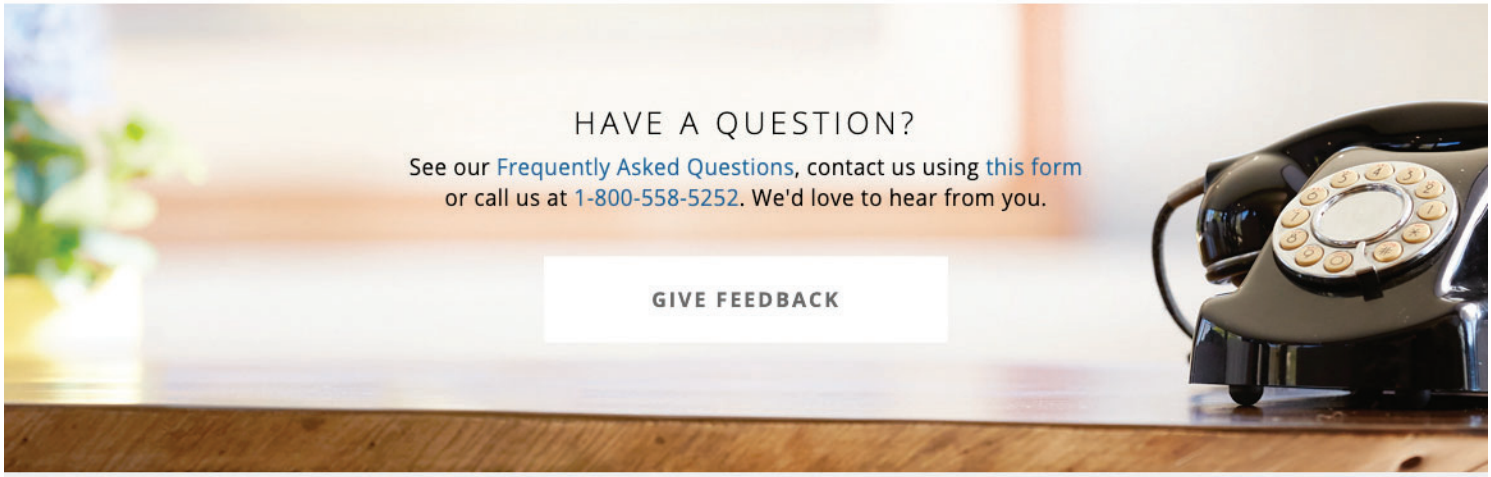
NEW! MORE FRAGRANCE DISCLOSURE

SC Johnson is the first major company to offer product-specific fragrance disclosure. We started with air care products in the U.S. and Canada, and we'll be adding other product categories soon.

Our goal is to list all ingredients down to .09 percent of the product formula. If that doesn't provide at least 10 ingredients, we will list the top 10 if there are at least 20 fragrance ingredients present.

We will always try to select the method of disclosure that gives you the longest list and the most information.

While they aren't disclosed, the remaining ingredients also must meet our strict standards and be approved as part of our fragrance palette in order to be used. You can learn more about our palette here.



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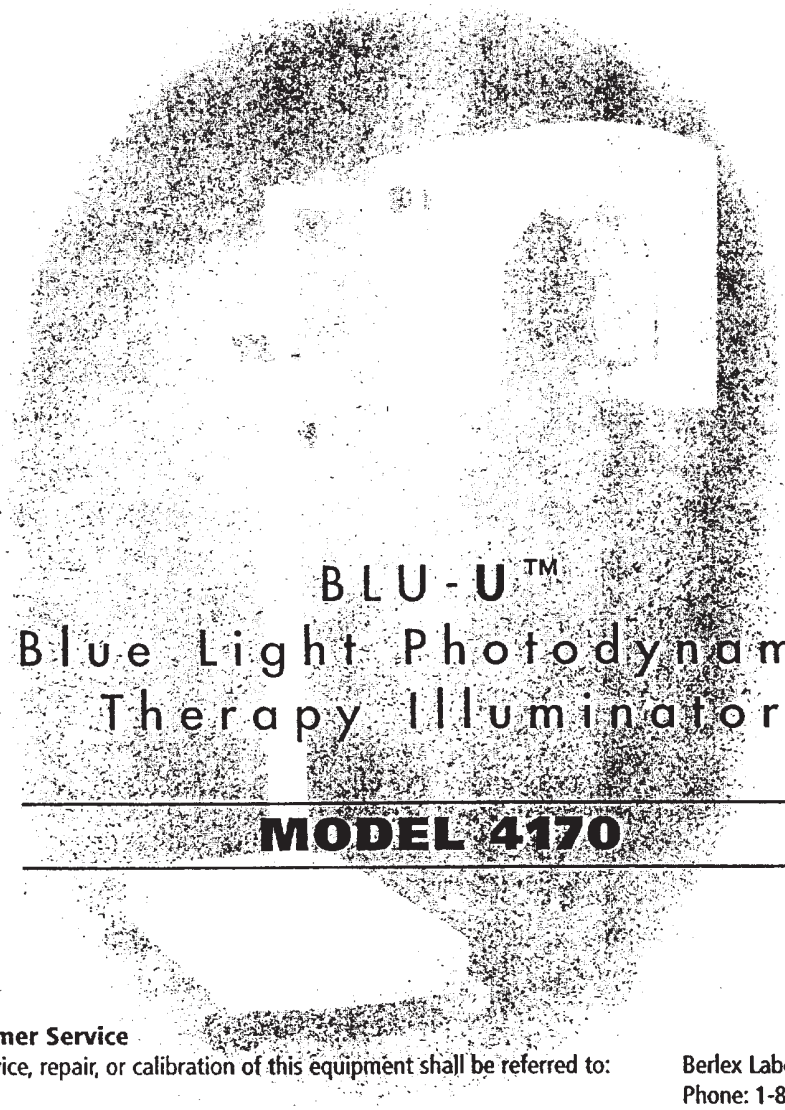
OPERATING MANUAL



BLU-U™
Blue Light Photodynamic Therapy Illuminator

MODEL 4170

Customer Service
All service, repair, or calibration of this equipment shall be referred to:

Berlex Laboratories
Phone: 1-888-BERLEX4

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OPERATING MANUAL
BLU-U™ Blue Light Photodynamic Therapy Illuminator
Model 4170

INDICATIONS FOR USE

DUSA Pharmaceuticals' **BLU-U™** blue light photodynamic therapy illuminator Model 4170, in combination with the Levulan® Kerastick™ (aminolevulinic acid HCl) for Topical Solution, 20%, is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp.

*Le dispositif d'éclairage **BLU-U™** à lumière bleue de DUSA Pharmaceuticals, destiné à un usage thérapeutique photodynamique et utilisé avec Levulan® Kerastick™ pour Solution Topique, est indiqué pour le traitement des kératoses actiniques non hyperkératotiques du visage ou du cuir chevelu.*

CAUTIONS AND WARNINGS

CAUTION!

Federal law restricts this device to sale to or use by or on the order of a physician.

AVERTISSEMENT!

Conformément à la législation des Etats Unis, seul un médecin peut acheter, utiliser ou donner l'ordre d'utiliser ce dispositif.

WARNING!

The BLU-U™ blue light photodynamic therapy illuminator, in combination with the Levulan® Kerastick™ for Topical Solution, is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp. Do not use this device with other photosensitizing drugs. Refer to the Levulan Kerastick for Topical Solution package insert for additional information.

The patient and all medical personnel should wear protective eyewear at all times during operation of the BLU-U. Use only eyewear which blocks light with wavelengths of at least 500 nm and shorter with an Optical Density (O.D.) of two or greater.

ATTENTION!

Le dispositif d'éclairage BLU-U™ à lumière bleue, destiné à un usage thérapeutique photodynamique et utilisé avec Levulan® Kerastick™ pour Solution Topique, est indiqué pour le traitement des kératoses actiniques non hyperkératotiques du visage ou du cuir chevelu. En aucun cas, il ne doit être utilisé avec d'autres médicaments photosensibil-

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isants. Reportez-vous à la notice de Levulan Kerastick pour Solution Topique pour toutes informations complémentaires.

Le patient ainsi que l'ensemble du personnel médical doivent porter des lunettes de protection pendant toute la durée de fonctionnement du dispositif BLU-U. N'utilisez que des lunettes qui arrêtent les rayons lumineux ayant une longueur d'onde d'au moins 500 nm et une densité optique de deux ou plus.

PRODUCT SPECIFICATIONS

The BLU-U is an electrical Class I, Type B device designed for indoor use only. It has been tested to the following standards: UL2606.1 and CAN/CSA C22.2 No.601.1:1994. General specifications are listed below.

Power cord	3-conductor hospital grade electrical cord
Power requirements	120 VAC 2.5 Amp 60 Hz
Footprint (light unit + stand)	39.25" W 26.5" D 50" min; 63" max H
Overall dimensions of the light unit	20.75" W 18.75" D 15.25" H
Weight (light unit + stand)	160 lbs.
Operating Temperature Range	20 – 30° C (68 – 86° F)

DESCRIPTION

The **BLU-U** is a compact light source designed to provide a uniform distribution of blue light to areas of the patient's face or scalp for the use stated above. It is comprised of 7 horizontally mounted U-shaped fluorescent tubes within a plastic chassis. The tubes are covered by a polycarbonate shield, which directs cooling airflow within the unit and significantly minimizes the risk of glass-patient contact in the event of tube breakage.

The **BLU-U** is mounted on a floor-stand, which permits rapid positioning for AK lesions located on the face or scalp, as well as adjustment for patient height. The control panel is also affixed to the floor stand.

The **BLU-U** has a built-in power output monitoring and diagnostic system, which illuminates a neon light to inform the user of the system's status.

The **BLU-U** has a system timer used to set the light dose delivered to the patient.

CONTROLS

Controls for the **BLU-U** are located on the floor stand.

Main Power Switch

The Main Power Switch is a two position rocker switch, labeled **"I"** and **"0"** located next to the electrical cord.

I = ON
0 = OFF

Push the **Main Power Switch** to "I" to turn on power to the system.
Push the **Main Power Switch** to "0" to disconnect all electrical components within the **BLU-U** from the AC line.

Key Switch

The **Key Switch** is the "ON/OFF" switch for the **BLU-U** and requires a special key to operate. Remove the key and store it securely whenever the unit is not in use, to prevent unauthorized use of the **BLU-U**.

Turn the **Key Switch** to **"I"** to turn on power to the **BLU-U** control electronics. This activates the **Timer** so that the prescribed exposure time can be entered. When activated, the timer will remem-

ber and display the last treatment time setting.

Note
When the Key Switch is turned off, it should not be turned back on again for at least five (5) seconds to ensure that the control electronics have properly powered down and reset.

Timer

The system **Timer** is used to control the operation of the fluorescent tubes. Use the **Timer** to:

- Set the exposure time,
- Initiate light exposure,

and after the set exposure time has elapsed,

- Automatically turn off the tubes.

The following buttons control operation of the Timer:

Button	**Function / Operation**
Time Select	**The Time Select buttons are used to set the exposure time.** Depress the UP ARROW button to increase time. Depress the DOWN ARROW button to decrease time. When first depressed, these buttons change the displayed reading slowly; if they remained depressed, the display changes quickly. Depressing and releasing these buttons quickly makes small adjustments to the displayed time.
Start/Stop	**The Start/Stop button toggles between the running and stopped states of the Timer and Tubes.** After the exposure time has been set, depress this button once to turn on the tubes and initiate the **Timer** countdown sequence. Depress it a second time to turn off the tubes and stop the **Timer**.

Note
If the light treatment is interrupted, see the Levulan Kerastick package insert for further details before proceeding.

Indicator Lights

Indicator lights for the **BLU-U** are located on the control panel on the floor stand.

Indicator	**Function / Operation**
System Status Indicator	The red neon light, located to the right of the **Timer**, indicates system status. At the beginning of each light treatment, the **System Status Indicator** flashes three (3) times to indicate that the system control electronics and the neon light are functioning normally, and that the **BLU-U** is ready for use.

If **System Status Indicator** light fails to flash three (3) times immediately after the initiation of timed light treatment, the **BLU-U** *should not be used* until the problem has been identified or a qualified service technician has serviced the unit. (See the **Troubleshooting Table**)

If a patient has been dosed with the Levulan Kerastick, see the Levulan Kerastick package insert for further instructions on early termination or cancellation of light treatment.
If the **System Status Indicator** lights at any other time, refer to **Table 1** below:

SYSTEM STATUS INDICATOR ERROR CONDITIONS

Table 1

Condition	**Action**
RAPID FLASHING Continuous rapid flashing of the **System Status Indicator** immediately after initiation of the timed light treatment indicates a problem with the electronic control system. If this happens, the **BLU-U** will not be operational and will not light.	Discontinue the treatment. Turn the **Key Switch** and the **Main Power Switch** to the **"0"** (off) position, and call DUSA's customer service department. *If the patient has been dosed with the Levulan Kerastick, see the Levulan Kerastick package insert for further instructions on early termination or cancellation of light treatment.*

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Slow Flashing Continuous slow flashing of the **System Status Indicator** (3 flashes every 4 seconds) after initiation of the timed light treatment indicates that either: • The **BLU-U** output power is too high, or • A problem exists with the **BLU-U**'s electronic control system.	Discontinue the treatment. Turn the **Key Switch** and the **Main Power Switch** to the **"0"** (off) position, and call DUSA's customer service department. *If the patient has been dosed with the Levulan Kerastick, see the Levulan Kerastick package insert for further instructions on early termination or cancellation of light treatment.*
Steady On The **System Status Indicator** lights steadily during the treatment (for at least 10 seconds at a time) This indicator code, which may occur after initiation of the timed light treatment, indicates that: • The **BLU-U** output power is too low, or • The end of tube lifetime has been reached.	• Complete the treatments of any patients who have already been dosed with the Levulan Kerastick, and • Call DUSA's customer service department.
Exposure Time Indicator	This four-digit red LED located on the Timer unit displays the remaining exposure time in minutes and seconds. Prior to pushing the Start button to begin light exposure, the display indicates the amount of exposure time set. When you press the Start button, the *Exposure Time Indicator* display counts down the amount of exposure time remaining. The tubes turn off automatically when the display reaches "00:00".

INSTRUCTIONS FOR USE

Note - If patient light treatment is interrupted, terminated prematurely, or cannot be administered, see the Levulan Kerastick package insert for important further instructions.

Initial Set-Up

1. Plug the female end of the supplied electrical cord into the mating jack on the floor stand base and plug the other end into a standard 120 VAC outlet.
2. Press the **Main Power Switch** to the **"I"** (on) position.

Set-Up

1. Using the key, turn the **Key Switch** to the **"I"** (on) position. Verify that the red **Timer** display is active.
2. Position the safety goggles on the patient prior to treatment. Place the safety goggles over the patient's eyes and insure the goggles are secure against the patient's face. Verify that the goggles do not cover or shadow any area intended for treatment.
3. Place the patient in an upright, sitting position. **The procedure for positioning the BLU-U depends on the location of the lesions to be treated and is found in the following 2 sections.** The patient's head may be supported during treatment. Ensure that the method of head support does not cover or shadow any area intended for treatment.

Procedure for Treating Lesions on the Face

1. Loosen the knobs on either side of the light unit and rotate it to the vertical position (the **"U"** shaped bulbs stacked vertically). Retighten the knobs to lock the light unit in place.
2. Position the **BLU-U** around the patient's head so the entire surface area to be treated lies between 2" and 4" from the BLU-U surface:

a.) The patient's nose should be **no closer** than 2" from the surface
and
b.) The patient's forehead and cheeks should be **no further** than 4" from the surface
and
c.) The sides of the patient's face and the patient's ears should be **no closer** than 2" from the **BLU-U** surface

Note:
The patient's hair should not cover or shadow the area to be treated. However, the patient's hair may be closer than 2" to the surface of the BLU-U without any deleterious effects.

3. Set the **Timer** to the prescribed treatment time of 16 minutes 40 seconds by depressing the *Time Select* buttons. Continue to depress these buttons until the correct time is displayed.
4. Insure that all personnel are wearing safety goggles and then depress the Start/Stop switch on the **BLU-U Timer**. The **System Status Indicator** will flash three (3) times and go off. If it does not flash three times, try the remedies in the **Troubleshooting Table**. If the **System Status Indicator** still does not flash three times, do not use the **BLU-U** even if the **Timer** works and the tubes light; system output may be incorrect under these circumstances. [See the Levulan Kerastick package insert for further instructions on cancellation of light treatment.]
5. Verify that all seven tubes are lit. If one or more does not light, discontinue the light treatment and call **for service**. See the Levulan Kerastick package insert for further details on early termination or cancellation of light treatment.
6. Periodically check the **System Status Indicator**. If the **System Status Indicator** lights during treatment, see "Indicator Lights" in the Controls section.
7. Take care that the patient does not move during the time the **BLU-U** is on as this may result in under exposure of the lesion(s).
At the end of the treatment period, the **Timer** will automatically turn off the **BLU-U**.

Following Patient Treatment

1. Remove the patient from the BLU-U and remove the patient's goggles.
2. Turn the **Key Switch** on the BLU-U to the "**0**" position
3. Remove the key from the BLU-U and store it in a secure location where unauthorized personnel cannot use it.

Procedure for Treating Lesions to the Scalp

Loosen the knobs on either side of the light unit and rotate it to the horizontal position (the 'U' shaped bulbs stacked horizontally). Retighten the knobs to lock the light unit in place.
Position the **BLU-U** around the patient's head so the entire surface area to be treated lies between 2" and 4" from the **BLU-U** surface:
a.) The patient's scalp should be **no closer** than 2" from the surface
and
b.) The patient's scalp should be **no further** than 4" from the surface
and
c.) The sides of the patient's face and the patient's ears should be **no closer** than 2" from the **BLU-U** surface

Note:
The patient's hair should not cover or shadow the area to be treated. However, the patient's hair may be closer than 2" to the surface of the BLU-U without any deleterious effects.

3. Set the **Timer** to the prescribed treatment time of 16 minutes 40 seconds by depressing the Time Select buttons. Continue to depress these buttons until the correct time is displayed.
4. Insure that all personnel are wearing safety goggles and then depress the Start/Stop switch on the **BLU-U Timer**. The **System Status Indicator** will flash three (3) times and goes off. If it does not flash three times, try the remedies in the ***Troubleshooting Table***. If the ***System Status Indicator*** still does not flash three times, do not use the **BLU-U** even if the **Timer** works and the tubes light; system output may be incorrect under these circumstances. [See the Levulan Kerastick package insert for further instructions on cancellation of light treatment.]
5. Verify that all seven tubes are lit. If one or more does not light, discontinue the light treatment and call DUSA's customer service department. See the Levulan Kerastick package insert for further details on early termination or cancellation of light treatment.
6. Periodically check the **System Status Indicator**. If the **System Status Indicator** lights during treatment, see "Indicator Lights" in the Controls section.
7. Take care that the patient does not move during the time the **BLU-U** is on as this may result in under exposure of the lesion(s).

At the end of the treatment period, the **Timer** will automatically turn off the **BLU-U**.

Following patient treatment

1. Remove the patient from the **BLU-U** and remove the patient's goggles.
2. Turn the **Key Switch** on the **BLU-U** to the "**O**" position.
3. Remove the key from the BLU-U and store it in a secure location where unauthorized personnel cannot use it.

Troubleshooting

The following chart has been included to assist in determining a solution for a problem or error. In all cases where the **BLU-U** is inoperable or patient light treatment is interrupted, refer to the Levulan Kerastick package insert for further instructions on early termination or cancellation of light treatment.

Symptom	Possible Cause	What To Do
No power / Fans not running / **No Timer** display upon turning **Key Switch** to the **"I"** (on) position.	**BLU-U** is not plugged in.	Verify that the **BLU-U** is plugged into a standard 120 VAC wall outlet.
	No power is present at the wall outlet	Verify that power is present at the outlet.
	Main Power Switch is not set to **"I"** (on).	Verify that the **Main Power Switch** is in the the **"I"** (on) position.
	Key Switch is not fully turned to **"I"** (on).	Verify that the **Key Switch** is in the **"I"** (on) position by rotating it clockwise 1/4 turn until a "click" is felt. If the fans now run, but the **Timer** still does not light or lights intermittently, there is an internal electrical fault. In this case use of the **BLU-U** will not be possible. Call for service.
	One or more fuses in the Fused Power Entry Module have blown.	Check the fuses in the Fused Power Entry Module, located next to the socket for the electrical cord on the base of the floor stand • Turn the **Key Switch** and **Main Power Switch** to the **"0"** (off) position • Unplug the unit • With a small screwdriver, slide out the fuse holder • Check the status of the two fuses. If either or both fuses are blown (as indicated by a break in the thin wire connecting the two metal ends of the fuse), replace with 5A 125 VAC fuses (0.5 x 20 mm fast acting, Bussman # GMA-5A) • Replace the fuse holder • Plug the unit into a standard 120 VAC wall outlet

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Symptom	Possible Cause	What To Do
		• Turn the **Main Power Switch** and **Key Switch** to the "**I**" (on) position. If normal operation does not resume or the fuse continues to blow, there is an internal electrical fault. In this case use of the **BLU-U** will not be possible. Call for service
	Internal electrical fault.	Use of the **BLU-U** will not be possible. Call for service.
System Status Indicator does not flash three (3) times when the **Start/Stop button on the Timer is pressed**	Neon light or control circuitry is not functioning properly.	Discontinue use of the **BLU-U.** Call for service.
System Status Indicator rapidly flashing –Tubes not lit	Control circuitry is not functioning properly.	Use of the **BLU-U** will not be possible. Call for service.
System Status Indicator slowly flashing –Tubes lit	Power output is above specified range.	Discontinue use of the **BLU-U.** Call for service
	Control circuitry is not functioning properly.	Discontinue use of the **BLU-U.** Call for service.
System Status Indicator on steady	Power below specified range	Complete treatment of patients already dosed with the Levulan Kerastick.

Symptom	Possible Cause	What To Do
or intermittently –Tubes lit		Call for service.
Tubes not all lit	Tube(s) cracked or broken.	Discontinue use of the **BLU-U**. Call for service.
	Control circuitry is not functioning properly.	Discontinue use of the **BLU-U**. Call for service.
F001 Error Code Displayed on **Timer**	**Timer** error	With the Key Switch turned to **"I"** (on), press the Start/Stop button to clear the **Timer** display.
F101 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.
F002 Error Code Displayed on **Timer**	**Timer** error	With the **Key Switch** turned to **"I"** (on), press the *Start/Stop* button to clear the **Timer** display.
F202 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.
F303 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.

Customer Service
All service, repair, or calibration of this equipment shall be referred to:
Berlex Laboratories
Phone:1-888-BERLEX4

Warranty Coverage and Disclaimers:
See the Terms and Conditions of your contract for specific information.

Manufactured for:
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25 Upton Drive
Wilmington, MA 01887

MAN-00000150 Rev. A Printed in USA

https://web.archive.org/web/20170218052144/http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20965slr003_levulan_lbl.pdf

Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

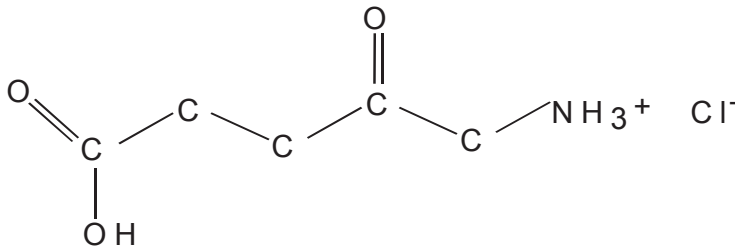
For Topical Use Only • Not for Ophthalmic Use

DESCRIPTION

LEVULAN® KERASTICK® (aminolevulinic acid HCl) for Topical Solution, 20%, contains the hydrochloride salt of aminolevulinic acid (ALA), an endogenous 5-carbon aminoketone.

Aminolevulinic acid HCl (ALA HCl) is a white to off-white, odorless crystalline solid that is very soluble in water, slightly soluble in methanol and ethanol, and practically insoluble in chloroform, hexane and mineral oil.

The chemical name for ALA HCl is 5-amino-4-oxopentanoic acid hydrochloride (MW = 167.59). The structural formula is represented below:



The LEVULAN KERASTICK for Topical Solution applicator is a two component system consisting of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle comprising alcohol USP (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of ALA HCl as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. The 20% topical solution is prepared just prior to the time of use by breaking the ampules and mixing the contents by shaking the LEVULAN KERASTICK applicator. The term “ALA HCl” refers to unformulated active ingredient, “LEVULAN KERASTICK for Topical Solution” refers to the drug product in its unmixed state, “LEVULAN KERASTICK Topical Solution” refers to the mixed drug product (in the applicator tube or after application), and “LEVULAN KERASTICK” refers to the applicator only.

CLINICAL PHARMACOLOGY

Pharmacology: The metabolism of aminolevulinic acid (ALA) is the first step in the biochemical pathway resulting in heme synthesis. Aminolevulinic acid is not a photosensitizer, but rather a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. The synthesis of ALA is normally tightly controlled by feedback inhibition of the enzyme, ALA synthetase, presumably by intracellular heme levels. ALA, when provided to the cell, bypasses this control point and results in the accumulation of PpIX, which is converted into heme by ferrochelatase through the addition of iron to the PpIX nucleus.

According to the presumed mechanism of action, photosensitization following application of LEVULAN Topical Solution occurs through the metabolic conversion of ALA to PpIX, which accumulates in the skin to which LEVULAN Topical Solution has been applied. When exposed to light of appropriate wavelength and energy, the accumulated PpIX produces a photodynamic reaction, a cytotoxic process dependent upon the simultaneous presence of light and oxygen. The absorption of light results in an excited state of the porphyrin molecule, and subsequent spin transfer from PpIX to molecular oxygen generates singlet oxygen, which can further react to form superoxide and hydroxyl radicals. Photosensitization of actinic (solar) keratosis lesions using the LEVULAN KERASTICK, plus illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator (BLU-U), is the basis for LEVULAN photodynamic therapy (PDT).

Pharmacokinetics: In a human pharmacokinetic study (N=6) using a 128 mg dose of sterile intravenous ALA HCl and oral ALA HCl (equivalent to 100 mg ALA) in which plasma ALA and PpIX were measured, the mean half-life of ALA was 0.70 ± 0.18 h after the oral dose and 0.83 ± 0.05 h after the intravenous dose. The oral bioavailability of ALA was 50-60% with a mean Cmax of 4.65 ± 0.94 µg/mL. PpIX concentrations were low and were detectable only in 42% of the plasma samples. PpIX concentrations in plasma were quite low relative to ALA plasma concentrations, and were below the level of detection (10 ng/mL) after 10 to 12 hours.

ALA does not exhibit fluorescence, while PpIX has a high fluorescence yield. Time-dependent changes in surface fluorescence have been used to determine PpIX accumulation and clearance in actinic keratosis lesions and perilesional skin after application of LEVULAN Topical Solution in 12 patients. Peak fluorescence intensity was reached in 11 ± 1 h in actinic keratoses and 12 ± 1 h in perilesional skin. The mean clearance half-life of fluorescence for lesions was 30 ± 10 h and 28 ± 6 h for perilesional skin. The fluorescence in perilesional skin was similar to that in actinic keratoses. Therefore, LEVULAN Topical Solution should only be applied to the affected skin.

Clinical Studies: LEVULAN KERASTICK for Topical Solution, 20%, plus blue light at 6-10.9 J/cm2, has been used to treat actinic keratoses in 232 patients in six clinical trials. Phase 3 studies were two, identically designed, multicenter, two-arm studies using LEVULAN KERASTICK for Topical Solution applicators plus illumination from the BLU-U for 1000 seconds (16 min 40 sec) for a nominal exposure of 10 J/cm2. Patients were excluded from these studies who had a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, photodermatosis, or inherited or acquired coagulation defects. A minimum of 4 and a maximum of 15 clinically typical, discrete, (Grade 1 or 2, see table 2 for definition), target actinic keratosis lesions were identified. Target lesions on the face or on the scalp, but not in both locations in the same patient, received treatment. The patients were randomized to receive treatment either with the LEVULAN KERASTICK for Topical Solution plus BLU-U or vehicle plus BLU-U. Patients were randomized at a 3 to 1 LEVULAN to vehicle ratio. A total of 243 patients were enrolled in two Phase 3 studies (ALA-018, ALA-019). Lesions were designated as cleared (complete response) if the lesion had completely cleared and adherent scaling plaques of actinic keratoses were no longer evident on the surface of the treated skin when palpated. The percentage of patients in whom 75% or more of treated lesions were cleared, and the percentage of patients in whom 100% of treated lesions were cleared (Complete Responders), for each study at 8 weeks after treatment are shown in Table 1.

TABLE 1 Patient Responses at Week 8

	ALA-018		ALA-019	
	LEVULAN	Vehicle	LEVULAN	Vehicle
Patients with ≥ 75% of AK Leasions Cleared				
Total No. Patients	68/87 (78%)	6/29 (21%)	71/93 (76%)	8/32 (25%)
Patients with Face Lesions	57/71 (80%)	2/21 (10%)	57/67 (85%)	7/19 (37%)
Patients with Scalp Lesions	11/16 (69%)	4/8 (50%)	14/26 (54%)	1/13 (8%)
Complete Responders				
Total No. Patients	60/87 (69%)	4/29 (14%)	59/93 (63%)	4/32 (13%)
Patients with Face Lesions	49/71 (69%)	2/21 (10%)	47/67 (70%)	4/19 (21%)
Patients with Scalp Lesions	11/16 (69%)	2/8 (25%)	12/26 (46%)	0/13 (0%)

Because clinical studies ALA-018 and ALA-019 had identical protocols, the combined results from the two trials are shown in the following tables. For actinic keratoses with a variety of thicknesses (excluding very thick, Grade 3 actinic keratoses which were not studied in the phase 3 trials), LEVULAN KERASTICK for Topical Solution plus BLU-U is more effective than vehicle plus BLU-U, but as shown in Table 2, the percentage of lesions with complete responses at 8 weeks after treatment with LEVULAN KERASTICK for Topical Solution plus blue light illumination was lower for those lesions that were thicker at baseline. Efficacy of LEVULAN KERASTICK for Topical Solution plus BLU-U on higher grade lesions was not studied in the Phase 3 clinical efficacy trials.

TABLE 2 Lesions Complete Responses at Week 8 for different Lesion Grades

	LEVULAN	Vehicle
Lesion Grade 1	666/756 (88%)	122/302 (40%)

(Slightly palpable actinic keratoses: better felt than seen)		
Lesion Grade 2 (Moderately thick actinic keratoses: easily seen and felt)	495/632 (78%)	52/199 (26%)
Lesion Grade 3 (Very Thick and/or hyperkeratotic actinic keratosis)	0	0

Those patients who were not Complete Responders at week 8 had retreatment of the persistent target lesions at week 8. Among the patients undergoing retreatment, efficacy results seen at 12 weeks after the initial treatment, i.e., at 4 weeks after the second treatment, are shown in Table 3.

TABLE 3 Complete Responders at Week 12, among Patients Receiving Two Treatments

	LEVULAN	Vehicle
Total No. Patients	24/56 (43%)	2/49 (4%)
Patients with Face Lesions	21/40 (53%)	2/31 (6%)
Patients with Scalp Lesions	3/16 (19%)	0/18 (0%)

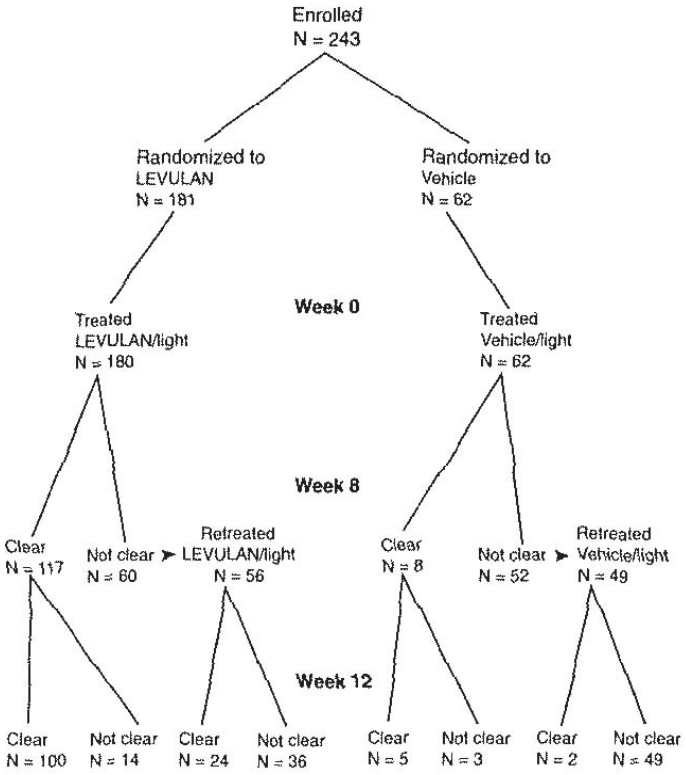
The efficacy results seen at 12 weeks after treatment, which include the results at 12 weeks for those patients who received a single treatment as well as the results at 12 weeks for those patients who received a second treatment at week 8, are shown in Table 4.

TABLE 4 Patient Responses at Week 12, among Patients who Received One or Two Treatments

	LEVULAN	Vehicle
	Patients with $\geq$ 75% of AK Leasions Cleared	
Total No. Patients	158/180 (88%)	12/61 (20%)
Patients with Face Lesions	127/138 (92%)	8/40 (20%)
Patients with Scalp Lesions	31/42 (74%)	4/21 (19%)
	Complete Responders	
Total No. Patients	129/180 (72%)	7/61 (11%)
Patients with Face Lesions	108/138 (78%)	5/40 (13%)
Patients with Scalp Lesions	21/42 (50%)	2/21 (10%)

Among Complete Responders at week 8, 93% (in study ALA-018) and 83% (in study ALA-019) maintained complete response at week 12. Among patients with scalp lesions, the percentage of patients with 100% of AK lesions having complete response declined from week 8 (55%) to week 12 (50%), because there were more patients with scalp lesions with 100% of AK lesions cleared at week 8 who had a recurrence of a lesion by week 12 than there were patients with scalp lesions who had retreatment of persistent lesions at week 8 and who then achieved 100% of AK lesions cleared by week 12. Patients did not receive follow-up past 12 weeks after the initial treatment.

Patient outcomes recorded in the two Phase 3 trials are depicted in the following flowchart, in which Complete Responders are designated clear. Seven patients in the active treatment arm and three patients in the vehicle treatment arm withdrew or were lost to follow-up, and their outcomes are not included in the flowchart. Three patients in the active treatment arm were treated at baseline but did not return for evaluation until week 12. One patient in the active treatment arm and two in the vehicle treatment arm who were not clear at week 8 did not receive retreatment.



INDICATIONS AND USAGE

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 keratosis (Grade 1 or 2, see table 2 for definition**)** of the face and scalp.

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.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK for Topical Solution should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

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

Information for Patients:

LEVULAN Photodynamic Therapy for Actinic Keratoses.

The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK for Topical Solution to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK for Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

Photosensitivity

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitive actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

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.

Carcinogenesis, Mutagenesis, Impairment to Fertility: No carcinogenicity testing has been carried out using ALA. No evidence of mutagenic effects was seen in four studies conducted with ALA to evaluate this potential. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK± mouse lymphoma forward mutation assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these in vitro studies. In the in vivo mouse micronucleus assay, ALA was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA exposure with PpIX formation. Other studies have documented oxidative DNA damage in vivo and in vitro as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

Pregnancy Category C: Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

Photodynamic Therapy Response: 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. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the 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 majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

The most common changes in lesion appearance after LEVULAN KERASTICK for 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. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

Other Localized Cutaneous Adverse Experiences: Table 5 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

TABLE 5 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019								
	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/ Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0%

Adverse Experiences Reported by Body System: In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose: LEVULAN KERASTICK Topical Solution overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose: There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

DOSAGE AND ADMINISTRATION

LEVULAN KERASTICK for Topical Solution is intended for direct application to individual lesions diagnosed as actinic keratoses and not to perilesional skin. This product is not intended for application by patients or unqualified medical personnel. Application should involve either scalp or face lesions, but not both simultaneously. The recommended treatment frequency is: one application of the LEVULAN Topical Solution and one dose of illumination per treatment site per 8-week treatment session. Each individual LEVULAN KERASTICK should be used for only one patient. Photodynamic therapy for actinic keratoses with LEVULAN KERASTICK for Topical Solution is a two stage process involving a) application of the product to the target lesions with LEVULAN KERASTICK, followed 14 to 18 hours later by b) illumination with blue light using the BLU-U Blue Light Photodynamic Therapy Illuminator. The second visit, for illumination, must take place in the 14-18 hour window following application. Patients in clinical trials usually received application in the late afternoon, with illumination the following morning.

TABLE 6 Schedule for LEVULAN and Blue Light Administration

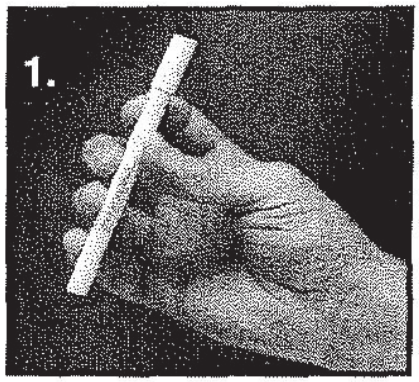
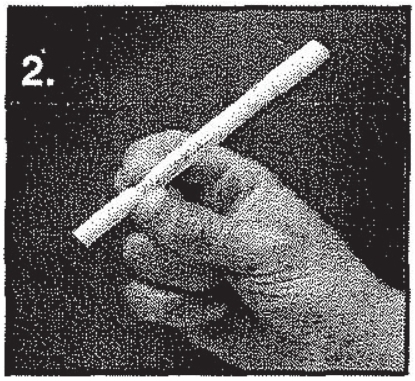
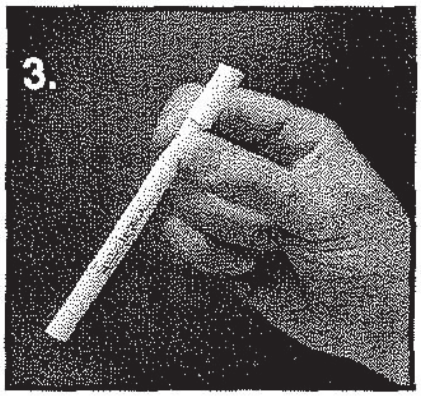
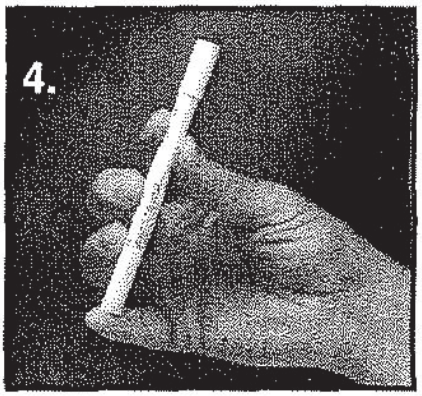
LEVULAN KERASTICK Topical Solution Application	Time Window for Blue Light Illumination
6 am	8 pm to Midnight
7 am	9 pm to 1 am
8 am	10 pm to 2 am
9 am	11 pm to 3 am
10 am	Midnight to 4 am
11 am	1 am to 5 am
12 pm	2 am to 6 am
1 pm	3 am to 7 am
2 pm	4 am to 8 am
3 pm	5 am to 9 am
4 pm	6 am to 10 am
5 pm	7 am to 11 am
6 pm	8 am to Noon
7 pm	9 am to 1 pm
8 pm	10 am to 2 pm
9 pm	11 am to 3 pm
10 pm	Noon to 4 pm

Treated lesions that have not completely resolved after 8 weeks may be treated a second time with LEVULAN KERASTICK for Topical Solution Photodynamic Therapy. Patients did not receive follow-up past 12 weeks after the initial treatment, so the incidence of recurrence of treated lesions past 12 weeks and the role of further treatment is not known.

Step A - LEVULAN KERASTICK for Topical Solution Application: Actinic keratoses targeted for treatment should be clean and dry prior to application of LEVULAN KERASTICK for Topical Solution.

Preparation:

The LEVULAN KERASTICK Topical Solution should be prepared as follows:

	
1. Hold the LEVULAN KERASTICK so that the applicator cap is pointing up.	2. Crush the bottom ampule containing the solution vehicle by applying finger pressure to Position A on the cardboard sleeve.
	
3. Crush the top ampule containing the ALA HCl powder by applying finger pressure to Position B on the cardboard sleeve. NOTE: To ensure both ampules are crushed continue crushing the applicator downward, applying finger pressure to Position A.	4. Holding the LEVULAN KERASTICK between the thumb and forefinger, point the applicator cap away from the face, shake the LEVULAN KERASTICK gently for at least 3 minutes to completely dissolve the drug powder in the solution vehicle.

LEVULAN KERASTICK Preparation: Following solution admixture, remove the cap from the LEVULAN KERASTICK. The dry applicator tip should be dabbed on a gauze pad until uniformly wet with solution.

Application:

Apply the solution directly to the target lesions by dabbing gently with the wet applicator tip. Enough solution should be applied to uniformly wet the lesion surface, including the edges without excess running or dripping. The effect of LEVULAN KERASTICK Topical Solution on ocular tissues is unknown. LEVULAN KERASTICK Topical Solution should not be applied to the periorbital area or allowed to contact ocular or mucosal surfaces. Once the initial application has dried, apply again in the same manner. The LEVULAN KERASTICK Topical Solution must be used immediately following preparation (dissolution) due to the instability of the activated product. If the solution application is not completed within 2 hours of activation, the applicator should be discarded and a new LEVULAN KERASTICK for Topical Solution used.

Photosensitization of the treated lesions will take place over the next 14-18 hours. The actinic keratoses should not be washed during this time. The patient should be advised to wear a wide-brimmed hat or other protective apparel to shade the treated actinic keratosis lesions from sunlight or other bright light sources until BLU-U treatment. The patient should be advised to reduce light exposure if the sensations of stinging and/or burning are experienced.

If for any reason the patient cannot be given BLU-U treatment during the prescribed time after LEVULAN KERASTICK Topical Solution application, he or she may nonetheless experience sensations of stinging and/or burning if the photosensitized actinic keratoses are exposed to sunlight or prolonged or intense light at that time. The patient should be advised to wear a wide-brimmed hat or other protective apparel to shade the treated actinic keratosis lesions from sunlight or other bright light sources until at least 40 hours after the application of LEVULAN KERASTICK Topical Solution. The patient should be advised to reduce light exposure if the sensations of stinging and/or burning are experienced.

Step B - Administration of BLU-U Treatment 14 to 18 hours after application of LEVULAN KERASTICK Topical Solution: At the visit for light illumination, the actinic keratoses to be treated should be gently rinsed with water and patted dry. Photoactivation of actinic keratoses treated with LEVULAN KERASTICK Topical Solution is accomplished with BLU-U illumination from the BLU-U Blue Light Photodynamic Therapy Illuminator. A 1000 second (16 minutes 40 seconds) exposure is required to provide a 10 J/cm2 light dose. During light treatment, both patients and medical personnel should be provided with blue blocking protective eyewear, as specified In the BLU-U Operating Instructions, to minimize ocular exposure. Please refer to the BLU-U Operating Instructions for further information on conducting the light treatment. Patients should be advised that transient stinging and/or burning at the target lesion sites occurs during the period of light exposure.

If blue light treatment with the BLU-U Blue Light Photodynamic Therapy Illuminator is interrupted or stopped for any reason, it should not be restarted and the patient should be advised to protect the treated lesions from exposure to sunlight or prolonged or intense light for at least 40 hours after application of the LEVULAN KERASTICK Topical Solution from the first visit.

For patients with facial lesions:

1.The BLU-U Blue Light Photodynamic Therapy Illuminator is positioned so that the base is slightly above the patient's shoulder, parallel to the patient's face.
2. The BLU-U is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the BLU-U surface:
   a) The patient's nose should be no closer than 2" from the surface;
   b) The patient's forehead and cheeks should be no further than 4" from the surface;
   c) The sides of the patient's face and the patient's ears should be no closer than 2" from the BLU-U surface.

A Chin Rest, available from DUSA Pharmaceuticals, Inc., may be used to provide support for the patient's head during treatment.

For patients with scalp lesions:

1. The knobs on either side of the BLU-U are loosened and the BLU-U is rotated to a horizontal position.
2. The BLU-U is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the BLU-U surface:
   a) The patient's scalp should be no closer than 2" from the surface;
   b) The patient's scalp should be no further than 4" from the surface;
   c) The sides of the patient's face and the patient's ears should be no closer than 2" from the BLU-U surface.

A Chin Rest, available from DUSA Pharmaceuticals, Inc., may be used to provide support for the patient's head during treatment.

LEVULAN KERASTICK for Topical Solution is not intended for use with any device other than the BLU-U Blue Light Photodynamic Therapy Illuminator. Use of LEVULAN KERASTICK for Topical Solution without subsequent BLU-U illumination is not recommended.

HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a singleunit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle. The other ampule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

Product Package	**NDC number**
Individual LEVULAN KERASTICK for Topical Solution, 20%	50419-810-01
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20%	50419-810-06

Storage Conditions: Store at 25°C (77°F); excursions permitted to 15 – 30°C (59° – 86°F). The LEVULAN KERASTICK for Topical Solution should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution used, if needed.

Manufactured by: North Safety Products
Cranston, RI 02921

Manufactured for: DUSA Pharmaceuticals, Inc.
Wilmington, MA 01887

Distributed by: BERLEX®

Berlex Laboratories
Wayne, NJ 07470

Revision: March 1, 2002 605810

For more information please contact:

BERLEX®

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www.berlex.com

https://web.archive.org/web/20161020085420/https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208081s000lbl.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AMELUZ® (aminolevulinic acid hydrochloride) gel, 10%, for topical use
Initial U.S. approval: 1999

----------INDICATIONS AND USAGE----------

AMELUZ gel, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED lamp, is indicated for the lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp (1).

----------DOSAGE AND ADMINISTRATION----------

- Administer AMELUZ only by a health care provider (2.1).
- AMELUZ is for topical use only (2.1).
- Photodynamic therapy with AMELUZ involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED (2.2).
- Retreat lesions that have not completely resolved 3 months after the initial treatment (2.2).
- See BF-RhodoLED user manual for detailed lamp safety and operating instructions (2).

----------DOSAGE FORMS AND STRENGTHS----------

Gel: 10% (3).

----------CONTRAINDICATIONS----------

- Known hypersensitivity to porphyrins (4).
- Known hypersensitivity to any component of AMELUZ, which includes soybean phosphatidylcholine (4).
- Porphyria (4).
- Photodermatoses (4).

----------WARNINGS AND PRECAUTIONS----------

- *Risk of Eye Injury:* Patients and healthcare providers must wear protective eyewear before operating BF-RhodoLED lamp (5.1).
- *Photosensitivity:* Protect treated lesions from sunlight exposure for 48 hours post treatment (5.2).
- *Risk of Bleeding:* Special care should be taken to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders (5.3).
- *Ophthalmic Adverse Reactions:* Avoid direct contact of AMELUZ with the eyes (5.4).
- *Mucous Membranes Irritation:* Avoid direct contact of AMELUZ with the mucous membranes (5.5).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 10%) were application site erythema, pain/burning, irritation, edema, pruritus, exfoliation, scab, induration, and vesicles (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Biofrontera Inc. at 1-884-829-7434 or FDA at 1-800-332-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Concomitant use of the following medications may enhance the phototoxic reaction to photodynamic therapy: St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines (7).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AMELUZ® gel, in combination with photodynamic therapy (PDT) using BF-RhodoLED® lamp, a narrowband, red light illumination source, is indicated for lesion-directed and field-directed treatment of actinic keratoses (AKs) of mild-to-moderate severity on the face and scalp.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

AMELUZ, in conjunction with lesion preparation, is only to be administered by a health care provider.

AMELUZ is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Treat single lesions or an entire field affected by multiple lesions with AMELUZ, in combination with red light photodynamic therapy (PDT). PDT requires administration of both AMELUZ and BF-RhodoLED light. Retreat lesions that have not completely resolved after 3 months after the initial treatment.

Refer to BF-RhodoLED user manual for detailed lamp safety and operating instructions. Both patient and medical personnel conducting the PDT should adhere to all safety instructions.

2.2 Dosage and Administration Instructions

PDT is a multi-stage process:

Step 1. Preparation of Lesions

Before applying AMELUZ, carefully wipe all lesions with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin.

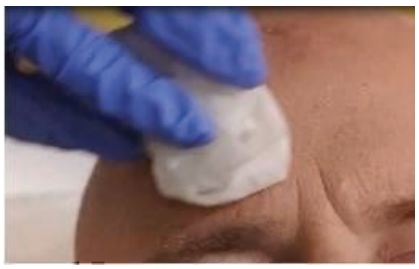


Figure 1A: Degreasing the skin

Thereafter, remove any scaling and crusts and gently roughen all lesion surfaces, taking care to avoid bleeding.

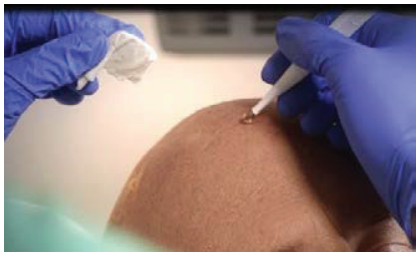


Figure 1B: Removal of scales and crust

Step 2. Application of AMELUZ

Use glove protected fingertips or a spatula to apply AMELUZ. Apply gel approximately 1 mm thick and include approximately 5 mm of the surrounding skin. Use sufficient amount of gel to cover the single lesions or if multiple lesions, the entire area. Application area should not exceed 20 cm^2 and no more than 2 grams of AMELUZ (one tube) should be used at one time. The gel can be applied to healthy skin around the lesions. Avoid application near mucous membranes such as the eyes, nostrils, mouth, and ears (keep a distance of 1 cm from these areas). In case of accidental contact with these areas, thoroughly rinse with water. Allow the gel to dry for approximately 10 minutes before applying occlusive dressing.

Figure 2: Drug application

Step 3. Occlusion for 3 Hours

Cover the area where the gel has been applied with a light-blocking, occlusive dressing. Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.

Figure 3: Occlusion

Step 4. Illumination with Red Light

During illumination, patient and medical personnel need to wear suitable protective eyewear.

Immediately after removing occlusion and any remaining gel, illuminate the treatment area with BF-RhodoLED®, a red light source with a narrow spectrum around 635 nm that delivers a light dose of approximately 37 J/cm^2 within 10 minutes. Calibration by the operator is not needed; the illumination time is calculated automatically. Position the lamp head 5-8 cm from the skin's surface. When an area of 8 x 18 cm is illuminated, the effective treatment area is 6 x16 cm. Larger areas can be illuminated in several steps.

Healthy untreated skin surrounding the AK lesions does not need protection during illumination.

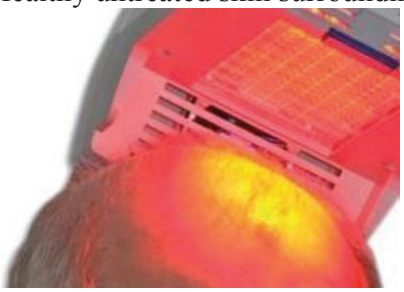


Figure 4: Illumination

If for any reason, the lesions cannot be illuminated within 3 hours after AMELUZ application, rinse off the gel with saline and water. For 2 days, protect the lesion sites and surrounding skin from sunlight or prolonged or intense light (e.g., tanning beds, sun lamps).

3. DOSAGE FORMS AND STRENGTHS

Each gram of AMELUZ gel, 10% contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid).

4. CONTRAINDICATIONS

AMELUZ is contraindicated in patients with:

- Known hypersensitivity to porphyrins.
- Known hypersensitivity to any of the components of AMELUZ, which includes soybean phosphatidylcholine.
- Porphyria. AMELUZ use may cause uncontrolled phototoxic effects *[see Warnings and Precautions (5.2)]*.
- Photodermatoses. PDT may worsen the phototoxic or photoallergic reactions *[see Warnings and Precautions (5.2)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Risk of BF-RhodoLED Lamp Induced Eye Injury

BF-RhodoLED lamp may cause eye irritation, glare, or injury. Before operating the lamp, personnel must refer to the user manual for specific warnings, cautions, and instructions. Eye exposure to the BF-RhodoLED light must be prevented. Protective eye equipment must be used by patient, healthcare providers and any person present during the illumination period. Avoid staring directly into the light source *[see Dosage and Administration (2)]*.

5.2 Increased Photosensitivity

AMELUZ increases photosensitivity. Avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on lesions and surrounding skin treated with AMELUZ for approximately 48 hours following treatment whether exposed to illumination or not. Concomitant use of AMELUZ

with other known photosensitizing agents may increase the risk of phototoxic reaction to PDT *[see Drug Interactions (7)]*.

5.3 Risk of Bleeding in Patients with Coagulation Disorders

AMELUZ has not been tested on patients with inherited or acquired coagulation disorders. Special care should be taken to avoid bleeding during lesion preparation in such patients *[see Dosage and Administration (2)]*. Any bleeding must be stopped before application of the gel.

5.4 Ophthalmic Adverse Reactions

Eyelid edema has occurred with AMELUZ application. AMELUZ can cause ophthalmic adverse reactions. AMELUZ is intended for topical use only. Do not apply AMELUZ into the eyes. Rinse eyes with water in case of accidental contact.

5.5 Risk of Mucous Membrane Irritation

AMELUZ can cause mucous membrane irritation. AMELUZ is intended for topical use only. Do not apply AMELUZ to the mucous membranes. Rinse with water in case of accidental contact.

6. ADVERSE REACTIONS

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

- Risk of BF-RhodoLED Lamp Induced Eye Injury*[see Warnings and Precautions (5.1)]*.
- Increased Photosensitivity *[see Warnings and Precautions (5.2)]*.
- Risk of Bleeding in Patients with Coagulation Disorders *[see Warnings and Precautions (5.3)]*.
- Ophthalmic Adverse Reactions *[see Warnings and Precautions (5.4)]*.
- Risk of Mucous Membranes Irritation *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trial 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 practice.

The clinical program for AMELUZ included three double-blind and placebo-controlled trials (Trials 1, 2, and 3), enrolling a total of 299 subjects that were treated with narrow band light. Trial subjects were adults greater than or equal to 49 years of age, and the majority had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

For all trials, the enrolled subjects had mild to moderate AKs (Olsen grade 1 and 2) with 4 to 8 lesions on the face and scalp. Overall, 87 placebo-treated subjects (n=16, n=32, n=39) and 212 AMELUZ-treated subjects (n=32, n=55, and n=125) were illuminated with BF-RhodoLED or similar narrow spectrum lamps.

Local skin reactions at the application site were observed in about 99.5% of subjects treated with AMELUZ and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema, pain, burning, irritation, edema, pruritus, exfoliation, scab, induration, and vesicles.

Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Severe pain/burning occurred in up to 30% of subjects. In one case, the adverse reactions required interruption or discontinuation of the illumination.

The incidence of common (≥1%, <10%) and very common (≥10%) adverse reactions in randomized, multicenter trials trials at the application site are presented in Table 1.

Table 1: Incidence of Adverse Reactions Occurring at ≥ 1% of the AMELUZ Group and More Frequently than the Vehicle Group in the Actinic Keratosis Trials at the Application Site

Adverse reaction	Vehicle n=87	AMELUZ n=212
Adverse reactions at the application site		
Erythema	34 (39%)	195 (92%)
Pain/Burning	26 (30%)	195 (92%)
Irritation	17 (20%)	153 (72%)
Edema	3 (3%)	75 (35%)
Pruritus	14 (16%)	72 (34%)
Exfoliation	4 (5%)	41 (19%)
Scab	2 (2%)	41 (19%)
Induration	0 (0%)	26 (12%)
Vesicles	1 (1%)	25 (12%)
Paresthesia	2 (2%)	18 (9%)
Hyperalgesia	0 (0%)	10 (5%)
Reaction	2 (2%)	8 (4%)
Discomfort	0 (0%)	7 (3%)
Erosion	0 (0%)	6 (3%)
Discharge	0 (0%)	4 (2%)
Bleeding	0 (0%)	3 (1%)
Pustules	0 (0%)	3 (1%)

Common (≥1%, < 10%) adverse reactions not limited to the application site were chills, headache, and skin exfoliation.

Uncommon (≥ 0.1%, <1%) adverse reactions at the application site for AMELUZ were hemorrhage and swelling. The adverse reactions not limited to the application site were eyelid edema, feeling hot, pain, pyrexia, ulcer, hyperalgesia, rash pustular, nervousness, blister, petechiae, pruritus, scab and skin erosion.

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid that were higher than doses normally used in the treatment of AK.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during post-approval use of AMELUZ outside the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: erythema, swelling, application site inflammation and skin discoloration.
Eye disorders: eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision.

7. DRUG INTERACTIONS

There have been no formal studies of the interaction of AMELUZ with other drugs. It is possible that concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT *[see Warnings and Precautions (5.1)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on AMELUZ use in pregnant women to inform a drug associated risk. Animal reproduction studies were not conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is negligible following topical administration of AMELUZ under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. It is not expected that maternal use of AMELUZ will result in fetal exposure to the drug.
The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of aminolevulinic acid in human milk, the effects of aminolevulinic acid on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the child to the drug due to the negligible systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMELUZ and any potential adverse effects on the breastfeeding child from AMELUZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established. AK is not a condition generally seen in the pediatric population.

8.5 Geriatric Use

Of the 384 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 83% (318/384) of the subjects were 65 years old and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

10. OVERDOSAGE

10.1 AMELUZ Overdose

AMELUZ overdosage following topical administration has not been reported. If AMELUZ is accidentally ingested, monitoring and supportive care is recommended. The patient should be advised to avoid incidental sunlight exposure for 48 hours after ingestion.

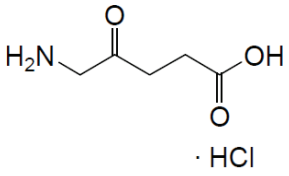
10.2 Red Light Overdose following AMELUZ Administration

There is no information on overdose of red light from the BF-RhodoLED following AMELUZ application.

11. DESCRIPTION

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% for topical use is a non-sterile white-to-yellowish gel. The gel formulation contains a nanoemulsion.

Aminolevulinic acid, a porphyrin precursor, is a white to off-white crystalline solid. It is readily soluble in water, methanol, and dimethylformamide. Its chemical name is 5-amino-4-oxo-pentanoic acid hydrochloride, molecular weight is 167.59 and molecular formula is $C_5H_9NO_3 \cdot HCl$. The structural formula of aminolevulinic acid hydrochloride is represented below:



Each gram of AMELUZ contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg aminolevulinic acid) as the active ingredient and the following inactive ingredients: xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, dibasic sodium phosphate, monobasic sodium phosphate, propylene glycol, sodium benzoate and purified water.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Photoactivation following topical application of AMELUZ occurs when aminolevulinic acid (prodrug) is metabolized to protoporphyrin IX (PpIX), a photoactive compound which accumulates in the skin. When exposed to red light of a suitable wavelength and energy, PpIX is activated resulting in an excited state of porphyrin molecules. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components, and eventually destroys the cells. AMELUZ photodynamic therapy of AK lesions utilizes photoactivation of topically applied AMELUZ resulting from BF-RhodoLED illumination, which provides a red light of narrow spectrum and a light dose of approximately 37 J/cm^2.

12.3 Pharmacokinetics

Pharmacokinetics (PK) of aminolevulinic acid and PpIX was evaluated in a trial of 12 adult subjects with mild to moderate AK with at least 10 AK lesions on the face or forehead. A single dose of one entire tube of AMELUZ (2 grams) was applied under occlusion for 3 hours followed by PDT to a total area of 20 cm^2. The mean ± SD baseline plasma aminolevulinic acid and PpIX concentrations were 20.16 ± 16.53 ng/mL and 3.27 ± 2.40 ng/mL, respectively. In most subjects, an up to 2.5-fold increase of aminolevulinic acid plasma concentrations was observed during the first 3 hours after AMELUZ application. The mean ± SD area under the concentration time curve (AUC_{0-t}) and maximum concentration (C_{max}) for baseline corrected aminolevulinic acid (n=12) were 142.83 ± 75.50 ng.h/mL and 27.19 ± 20.02 ng/mL, respectively. The median Tmax (time at which C_{max} occurred) was 3 hours.

The majority (about 55%) of the PpIX concentrations were below the limit of quantification (LOQ = 1 ng/mL) and baseline corrected values were negative in all subjects except for one. The baseline corrected AUC_{0-t} and C_{max} in the single subject was 0.07 ng.h/mL and 0.29 ng/mL, respectively. PK of aminolevulinic acid and PpIX following treatment on the scalp was not evaluated.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of AMELUZ or aminolevulinic acid have not been performed.

Aminolevulinic acid revealed no evidence of mutagenic or clastogenic potential based on the results of three in vitro genotoxicity tests (Ames assay, HPRT test in V79 cells, and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay). These genotoxicity studies were conducted without exposure to light. There is a literature report that indicates that aminolevulinic acid may cause genotoxic effects in the presence and in the absence of activating light. These genotoxic effects are likely caused by the formation of reactive oxygen species.

Animal fertility studies have not been conducted with aminolevulinic acid because of the negligible systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions.

14. CLINICAL STUDIES

The efficacy and safety of AMELUZ in combination with PDT using a narrow spectrum (red light lamp) source were evaluated in three randomized, multicenter trials (Trials 1, 2, and 3). Trials 2 and 3 were vehicle-controlled and double-blind. Trial 1 was double-blind with respect to vehicle and observer-blind regarding the active comparator arm. All clinical trials included a follow-up assessment after 6 and 12 months.

In these trials, 212 subjects with 4 to 8 mild to moderate AK lesions on the face/forehead and/or bald scalp were treated with AMELUZ and a narrow band spectrum lamp. Subjects ranged from 49 to 87 years of age (mean 71 years), and 92% had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

All sessions were comprised of lesion preparation to roughen the surface and remove crusts, application of AMELUZ with occlusion for 3 hours, and removal of the residual gel. Subsequently, the entire treatment area was illuminated with a narrow spectrum red light source, a lamp of either 630 nm or 633 nm and a light dose of approximately 37 J/cm^2. In Trial 3, illumination was performed with BF-RhodoLED, a red light source with a narrow spectrum around 635 nm and a light dose of approximately 37 J/cm^2.

In all trials, the lesions that were not completely cleared 12 weeks after the initial treatment were treated a second time with an identical regimen. In the trials, 42% (88/212) of subjects needed a second treatment.

The primary endpoint for all trials was complete clearance 12 weeks after the last PDT. The results of Trials 1, 2 and 3 are presented in Table 2.

Table 2: Complete Clearance 12 Weeks After the Last Narrow Spectrum PDT in Subjects with Actinic Keratoses

	Narrow Spectrum PDT	
	AMELUZ	Vehicle
Trial 1	106/125 (85%)	5/39 (13%)
Trial 2	27/32 (84%)	2/16 (13%)
Trial 3	50/55 (91%)	7/32 (22%)

Subjects who achieved complete clearance at 12 weeks after the last PDT entered a 12-month follow-up period. In the three trials, subjects who received AMELUZ with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT had recurrence rates of 14%, 11%, and 25%, respectively (at 6 months) and 40%, 22%, and 37%, respectively (at 12 months). Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow-up period in subjects with completely cleared lesions 12 weeks after the last PDT.

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid hydrochloride with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid hydrochloride that were higher than doses normally used in the treatment of AK.

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% is a white-to-yellowish gel. The drug product is supplied in an aluminum tube with a white, high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC 70621-101-01 2 g tube

Store AMELUZ in a refrigerator, 2°C– 8°C (36˚F - 46˚F). Excursions permitted to 15°C – 30°C (59°F -86°F).

After opening, AMELUZ can be stored for up to 12 weeks in a refrigerator at 2°C – 8°C (36˚F - 46˚F) if the tube is tightly closed.

17. PATIENT COUNSELING INFORMATION

17.1 Photosensitivity

Advise patients that for approximately 48 hours following treatment to avoid exposure to sunlight, and prolonged or intense light on the treated lesion sites and surrounding skin.

Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT *[see Warnings and Precautions (5) and Drug Interactions (7)]*.

17.2 Common Adverse Reactions

Inform patients that treatment with AMELUZ in combination with PDT may result in adverse reactions which include local skin reactions at the application site such as erythema, pain/burning, irritation, edema, pruritus, exfoliation, induration, scab, and vesicles.

AMELUZ and BF-RhodoLED are registered trade marks of Biofrontera Pharma GmbH.

PATENT INFO

US patent 6,559,183 and pending patent application US 2009/0324727

Distributed by:

Biofrontera Inc.

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Wakefield, MA 01880

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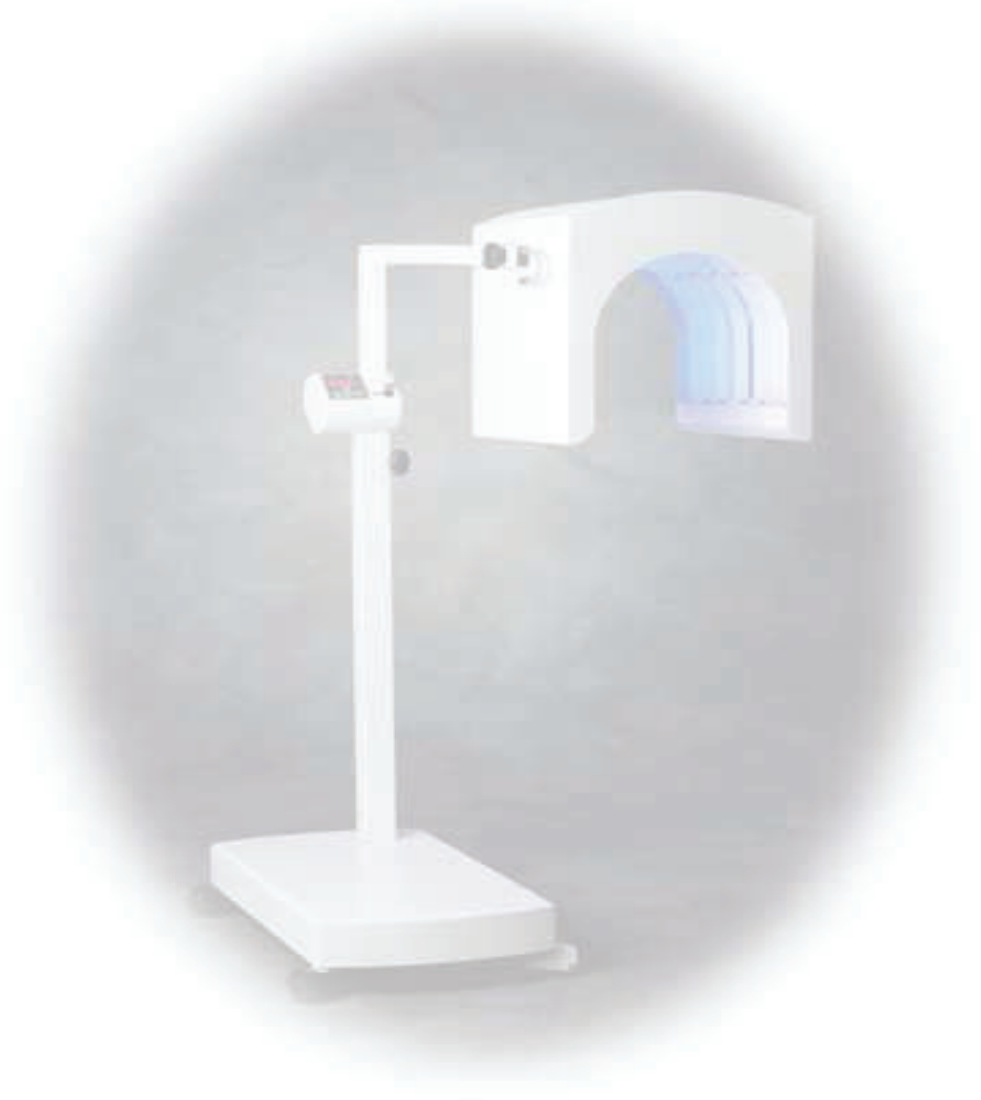
https://web.archive.org/web/20060311051209/http://www.dusapharma.com/pdf/MAN-1211_RevB_Operating%20Manual%20-%20English%20Version.pdf

DUSA®

Operating Manual



BLU-U® Blue Light Photodynamic Therapy
Illuminator Model 4170

Operating Manual

OPERATING MANUAL

BLU-U® Blue Light Photodynamic Therapy Illuminator
Model 4170

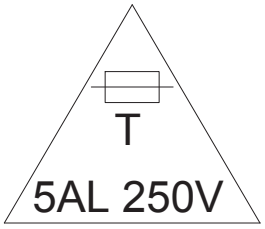
When Printed This Document is "For Reference Use Only"

Table of Contents

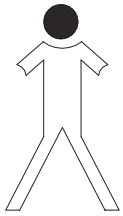
Symbols and Definitions:

Reference User Manual

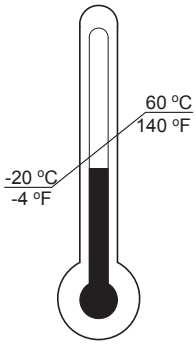
Warning/Caution



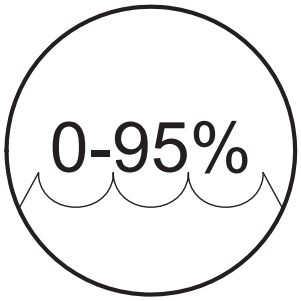
Indicates the Electrical Specification and Location of the Required Fuses



This Equipment Conforms to the IEC Publication 878-02-02 Type B Classification



Indicates the Upper and Lower Temperatures Allowed for Storage and Transport



Indicates the % Humidity Allowed for Storage and Transport

Indicates Need to Wear Eye Protection

Indications for Use:

DUSA Pharmaceuticals, Inc.® **BLU-U®** Blue Light Photodynamic Therapy Illuminator Model 4170, in combination with the Levulan® Kerastick® (aminolevulinic acid HCl) for Topical Solution, 20%, is indicated for the treatment of non-hyperkeratotic actinic keratoses (AK) of the face or scalp.

The **BLU-U®** Blue Light Photodynamic Therapy Illuminator Model 4170 is intended to provide phototherapeutic light to the body. The **BLU-U®** 4170 is generally indicated to treat dermatological indications. The **BLU-U®** 4170 is specifically indicated to treat moderate inflammatory acne vulgaris.

Cautions and Warnings:

WARNING: The **BLU-U®** Blue Light Photodynamic Therapy Illuminator, in combination with the Levulan® Kerastick® for Topical Solution, 20% is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp. Do not use this device with other photosensitizing drugs. Refer to the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for additional information. When using the **BLU-U®** for acne, do not use this device with photosensitizing drugs.
WARNING: All personnel should read and understand the instructions in this manual before the system is used. Failure to do so may result in improper operation of the system.
WARNING: Use only eyewear which blocks light with wavelengths of at least 500nm and shorter with an Optical Density (OD) of two or greater.
WARNING: To avoid risk of electrical shock, connect the power cord to a properly wired grounding receptacle only.
WARNING: Never attempt to service the device when it is connected to a power source. Hazardous voltages inside the device may cause severe electrical shock. Disconnect the power cord before servicing.
WARNING: Do not allow fluids to enter the device. Damage to the device may result.
CAUTION: The device should not be serviced or opened except by qualified service technicians. Tampering by unqualified persons may cause damage to the unit or personal injury.
CAUTION: Federal law restricts this device to sale by or on the order of a physician or licensed medical practitioner.

Product Specifications:

The **BLU-U®** is an electrical Class I, Type B device designed for indoor use only. It has been tested to the following standards: UL2606.1, CAN/CSA C22.2 No.601.1, EN60601-1, and EN 60601-1-2. General specifications are listed below.

Power cord	3-conductor hospital grade electrical cord
Power requirements	117 VAC, 2.5 Amps, 60 Hz
Footprint (light unit + stand)	Width: 99.70 cm (39.25 inches) Depth: 67.31 cm (26.5 inches) Height Minimum: 127 cm (50 inches) Height Maximum: 160 cm (63 inches)
Overall dimensions of the light unit	Width: 52.71 cm (20.75 inches) Depth: 47.63 cm (18.75 inches) Height: 38.74 cm (15.25 inches)
Weight (light unit + stand)	72.6 kg (160 lbs.)
Operating Temperature Range	20 – 30° C (68 – 86° F)

Description:

The **BLU-U®** is a compact light source designed to provide a uniform distribution of blue light to areas of the patient's face or scalp for the use stated above. It is comprised of 7 horizontally mounted U-shaped fluorescent tubes within a plastic chassis. The tubes are covered by a polycarbonate shield, which directs cooling airflow within the unit and significantly minimizes the risk of glass-patient contact in the event of tube breakage.

The **BLU-U®** is mounted on a floor-stand, which permits rapid positioning as well as adjustment for patient height. The control panel is also affixed to the floor stand.

The **BLU-U®** has a built-in power output monitoring and diagnostic system, which illuminates a neon light to inform the user of the system's status.

The **BLU-U®** has a system timer used to set the light dose delivered to the patient.

The **BLU-U®** is rated for short-time operation.

Controls:

Controls for the **BLU-U®** are located on the floor stand.

Main Power Switch:

The **Main Power Switch** is a two-position rocker switch, labeled "**I**" and "**0**," located next to the electrical cord.

I	=	ON
0	=	OFF

Push the **Main Power Switch** to "**I**" to turn on power to the system.
Push the **Main Power Switch** to "**0**" to disconnect all electrical components within the **BLU-U®** from the AC line.

Key Switch:

The **Key Switch** is the "ON/OFF" switch for the **BLU-U®** and requires a special key to operate.

➔ Remove the key and store it securely whenever the unit is not in use, to prevent unauthorized use of the **BLU-U®**.

Turn the **Key Switch** to "**I**" to turn on power to the **BLU-U®** control electronics. This activates the **Timer** so that the prescribed exposure time can be entered. When activated, the timer will remember and display the last treatment time setting.

Note:
When the Key Switch is turned off, it should not be turned back on again for at least thirty (30) seconds to ensure that the control electronics have properly powered down and reset.

Timer:

The system **Timer** is used to control the operation of the fluorescent tubes. Use the Timer to:

- Set the exposure time,
- Initiate light exposure,
  and after the set exposure time has elapsed,
- Automatically turn off the tubes.

The following buttons control operation of the Timer:

BUTTON	FUNCTION / OPERATION
Time Select ↑ ↓	**The Time Select buttons are used to set the exposure time**. Depress the ↑ (up arrow) button to increase time. Depress the ↓ (down arrow) button to decrease time. When first depressed, these buttons change the displayed reading slowly; if they remained depressed, the display changes quickly. Depressing and releasing these buttons quickly makes small adjustments to the displayed time.
Start/Stop	**The Start/Stop button toggles between the *running* and *stopped* states of the Timer and Tubes.** After the exposure time has been set, depress this button once to turn on the tubes and initiate the **Timer** countdown sequence. Depress it a second time to turn off the tubes and stop the **Timer**.

Note:
If the light treatment for actinic keratoses of the face or scalp is interrupted, see the Levulan® Kerastick® for Topical Solution, 20% package insert for further details before proceeding.

If the light treatment for acne is interrupted, reset and continue treatment.

Indicator Lights:

Indicator lights for the **BLU-U®** are located on the control panel on the floor stand.

INDICATOR	FUNCTION / OPERATION
System Status Indicator	The red neon light, located to the right of the **Timer**, indicates system status. At the beginning of each light treatment, the **System Status Indicator** flashes three (3) times to indicate that the system control electronics and the neon light are functioning normally, and that the **BLU-U®** is ready for use.

If **System Status Indicator** light fails to flash three (3) times immediately after the initiation of timed light treatment, the **BLU-U®** *should not be used* until the problem has been identified or a qualified service technician has serviced the unit.
(*See the* **Troubleshooting Table**)

If a patient has been dosed with the Levulan® Kerastick® for Topical Solution, 20%, for the treatment of actinic keratoses of the face or scalp, see the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further instructions on early termination or cancellation of light treatment.

If the **System Status Indicator** lights at any other time, refer to **Table 1** on the following page.

System Status Indicator Error Conditions:

Table 1

CONDITION	ACTION
Rapid Flashing Continuous rapid flashing of the **System Status Indicator** immediately after initiation of the timed light treatment indicates a problem with the electronic control system. If this happens, the **BLU-U®** will not be operational and will not light.	Discontinue the treatment. Turn the **Key Switch** and the **Main Power Switch** to the "**0**" (off) position, and call customer service. *If the patient has been dosed with the Levulan® Kerastick® for Topical Solution, 20%, see the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further instructions on early termination or cancellation of light treatment.*
Slow Flashing Continuous slow flashing of the **System Status Indicator** (3 flashes every 4 seconds) after initiation of the timed light treatment indicates that either: • The **BLU-U®** output power is too high, or • A problem exists with the **BLU-U®** electronic control system.	Discontinue the treatment. Turn the **Key Switch** and the **Main Power Switch** to the "**0**" (off) position, and call DUSA's customer service department. *If the patient has been dosed with the Levulan® Kerastick® for Topical Solution, 20%, see the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further instructions on early termination or cancellation of light treatment.*
Steady On The **System Status Indicator** lights steadily during the treatment (for at least 10 seconds at a time) This indicator code, which may occur after initiation of the timed light treatment, indicates that: • The **BLU-U®** output power is too low, or • The end of tube lifetime has been reached.	• Complete the treatments of any patients who have already been dosed with the Levulan® Kerastick®, and • Call customer service.
Exposure Time Indicator	This four-digit red LED located on the Timer unit displays the remaining exposure time in minutes and seconds. Prior to pushing the Start button to begin light exposure, the display indicates the amount of exposure time set. When you press the Start button, the *Exposure Time Indicator* display counts down the amount of exposure time remaining. The tubes turn off automatically when the display reaches "00:00".

Instructions for Use with the Levulan® Kerastick® for the treatment of Actinic Keratoses:

Note - If a patient's light treatment is interrupted, terminated prematurely, or cannot be administered, see the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for important further instructions.

Initial Set-Up:

1. Inspect the unit power fuse holder to ensure the correct line voltage has been selected.
2. Plug the female end of the supplied electrical cord into the mating jack on the floor stand base and plug the other end into a standard 120~ outlet.
3. Press the **Main Power Switch** to the "**I**" (on) position.

Set-Up:

1. Using the key, turn the **Key Switch** to the "**I**" (on) position. Verify that the red **Timer** display is active.
2. Position the eye protection on the patient prior to treatment. Place the eye protection over the patient's eyes and insure the eye protection is secure against the patient's face. Verify that the eye protection does not cover or shadow any area intended for treatment.
3. Place the patient in an upright, sitting position. **The procedure for positioning the BLU-U® depends on the location of the lesions to be treated and is found in the following 2 sections**. The patient's head may be supported during treatment. Ensure that the method of head support does not cover or shadow any area intended for treatment.

Procedure for Treating Lesions on the Face:

1. Loosen the knobs on either side of the light unit and rotate it to the vertical position (the "U" shaped bulbs stacked vertically). Retighten the knobs to lock the light unit in place.
2. Position the **BLU-U®** around the patient's head so the entire surface area to be treated lies between 2" and 4" from the **BLU-U®** surface:
   a.) The patient's nose should be ***no closer*** than 2" from the surface
   and
   b.) The patient's forehead and cheeks should be ***no further*** than 4" from the surface
   and
   c.) The sides of the patient's face and the patient's ears should be ***no closer*** than 2" from the **BLU-U®** surface

Note:
The patient's hair should not cover or shadow the area to be treated. However, the patient's hair may be closer than 2" to the surface of the BLU-U® without any deleterious effects.

3. Set the **Timer** to the prescribed treatment time of 16 minutes 40 seconds by depressing the *Time Select* buttons. Continue to depress these buttons until the correct time is displayed.

4. Insure that all personnel are wearing appropriate eye protection and then depress the *Start/Stop* switch on the **BLU-U® Timer**. The **System Status Indicator** will flash three (3) times and go off. *If it does not flash three times, try the remedies in the **Troubleshooting Table**. If the **System Status Indicator** still does not flash three times, do not use the **BLU-U®** even if the **Timer** works and the tubes light; system output may be incorrect under these circumstances. [See the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further instructions on cancellation of light treatment.]*

5. Verify that all seven tubes are lit. If one or more does not light, discontinue the light treatment and **call for service**. See the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further details on early termination or cancellation of light treatment.

6. Periodically check the **System Status Indicator**. If the **System Status Indicator** lights during treatment, see "Indicator Lights" in the Controls section.

7. Take care that the patient does not move during the time the **BLU-U®** is on as this may result in under exposure of the lesion(s).

8. At the end of the treatment period, the **Timer** will automatically turn off the **BLU-U®**.

Following Patient Treatment:

1. Remove the patient from the **BLU-U®** and remove the patient's eye protection.
2. Turn the **Key Switch** on the **BLU-U®** to the "**0**" position
3. Remove the key from the **BLU-U®** and store it in a secure location where unauthorized personnel cannot use it.

Procedure for Treating Lesions on the Scalp:

1. Loosen the knobs on either side of the light unit and rotate it to the horizontal position (the "U" shaped bulbs stacked horizontally). Retighten the knobs to lock the light unit in place.
2. Position the **BLU-U®** around the patient's head so the entire surface area to be treated lies between 2" and 4" from the **BLU-U®** surface:
   a.) The patient's scalp should be ***no closer*** than 2" from the surface
   and
   b.) The patient's scalp should be ***no further*** than 4" from the surface
   and
   c.) The sides of the patient's face and the patient's ears should be ***no closer*** than 2" from the **BLU-U®** surface

Note:
The patient's hair should not cover or shadow the area to be treated. However, the patient's hair may be closer than 2" to the surface of the BLU-U® without any deleterious effects.

3. Set the **Timer** to the prescribed treatment time of 16 minutes 40 seconds by depressing the *Time Select* buttons. Continue to depress these buttons until the correct time is displayed.

4. Insure that all personnel are wearing appropriate eye protection and then depress the *Start/Stop* switch on the **BLU-U® Timer.** The **System Status Indicator** will flash three (3) times and goes off. *If it does not flash three times, try the remedies in the **Troubleshooting Table**. If the **System Status Indicator** still does not flash three times, do not use the **BLU-U®** even if the **Timer** works and the tubes light; system output may be incorrect under these circumstances. [See the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further instructions on cancellation of light treatment.]*

5. Verify that all seven tubes are lit. If one or more does not light, discontinue the light treatment and call customer service. See the Levulan® Kerastick® for Topical Solution, 20% Package Physician Insert for further details on early termination or cancellation of light treatment.

6. Periodically check the **System Status Indicator**. If the **System Status Indicator** lights during treatment, see "Indicator Lights" in the Controls section.

7. Take care that the patient does not move during the time the **BLU-U®** is on as this may result in under exposure of the lesion(s).

8. At the end of the treatment period, the **Timer** will automatically turn off the **BLU-U®**.

Following patient treatment:

1. Remove the patient from the **BLU-U®** and remove the patient's eye protection.

2. Turn the **Key Switch** on the **BLU-U®** to the "**0**" position.

3. Remove the key from the **BLU-U®** and store it in a secure location where unauthorized personnel cannot use it.

Instructions for Use for the Light Only treatment of Acne:

Initial Set-Up:

1. Inspect the unit power fuse holder to ensure the correct line voltage has been selected.
2. Plug the female end of the supplied electrical cord into the mating jack on the floor stand base and plug the other end into a standard 120 ~ outlet.
3. Press the **Main Power Switch** to the "**I**" (on) position.

Set-Up:

1. Using the key, turn the **Key Switch** to the "**I**" (on) position. Verify that the red **Timer** display is active.
2. Position the eye protection on the patient prior to treatment. Place the eye protection over the patient's eyes and insure the eye protection is secure against the patient's face. Verify that the eye protection does not cover or shadow any area intended for treatment.
3. Place the patient in an upright, sitting position. The patient's head may be supported during treatment. Ensure that the method of head support does not cover or shadow any area intended for treatment.

Procedure for treating Acne:

1. Loosen the knobs on either side of the light unit and rotate it to the vertical position (the "U" shaped bulbs stacked vertically). Retighten the knobs to lock the light unit in place.
2. For treatment of the face, position the **BLU-U®** around the patient's head so the entire surface area to be treated lies between 2" and 4" from the **BLU-U®** surface:
   a.) The patient's nose should be ***no closer*** than 2" from the surface
   and
   b.) The patient's forehead and cheeks should be ***no further*** than 4" from the surface
   and
   c.) The sides of the patient's face and the patient's ears should be ***no closer*** than 2" from the **BLU-U®** surface

   Note:
   The patient's hair should not cover or shadow the area to be treated. However, the patient's hair may be closer than 2" to the surface of the BLU-U® without any deleterious effects.
3. Set the **Timer** for the desired treatment time by depressing the *Time Select* buttons. Continue to depress these buttons until the correct time is displayed. The recommended exposure time is 16 minutes and 40 seconds per treatment (10 joules/cm²). Light treatments should be performed two to three times per week until the desired clinical results have been achieved with a maximum recommended total cumulative light exposure of 320 joules/cm². Insure that all personnel are wearing appropriate eye protection and then depress the *Start/Stop* switch on the **BLU-U® Timer**. The **System Status Indicator** will flash three (3) times and go off. *If it does not flash three times, try the remedies in the **Troubleshooting Table**. If the **System***

Status Indicator *still does not flash three times, do not use the* ***BLU-U®*** *even if the* ***Timer*** *works and the tubes light; system output may be incorrect under these circumstances.*

4. Verify that all seven tubes are lit. If one or more does not light, discontinue the light treatment and **call for service**.
5. Periodically check the **System Status Indicator**. If the **System Status Indicator** lights during treatment, see “Indicator Lights” in the Controls section.
6. Take care to minimize patient movement during the time the **BLU-U®** is in use.
7. At the end of the treatment period, the **Timer** will automatically turn off the **BLU-U®**.

Following Patient Treatment:

1. Remove the patient from the **BLU-U®** and remove the patient’s eye protection.
2. Turn the **Key Switch** on the **BLU-U®** to the “**0**” position
3. Remove the key from the **BLU-U®** and store it in a secure location where unauthorized personnel cannot use it.

Troubleshooting/Service and Repair:

There are no service parts in the equipment.

CAUTION:

Components of the system should not be opened, except by a Qualified Service Person. Tampering by Unqualified Persons can harm the person and/or damage the unit.

The following chart has been included to assist in determining a solution for a problem or error

Symptom	Possible Cause	What To Do
No power / Fans not running / No **Timer** display upon turning **Key Switch** to the "**I**" (on) position.	**BLU-U®** is not plugged in.	Verify that the proper line voltage has been selected on the fuse holder. Verify that the **BLU-U®** is plugged into a standard 120 ~ wall outlet.
	No power is present at the wall outlet.	Verify that power is present at the outlet.
	Main Power Switch is not set to "**I**" (on).	Verify that the **Main Power Switch** is in the "**I**" (on) position.
	Key Switch is not fully turned to "**I**" (on).	Verify that the **Key Switch** is in the "**I**" (on) position by rotating it clockwise 1/4 turn until a "click" is felt. If the fans now run, but the **Timer** still does not light or lights intermittently, there is an internal electrical fault. In this case use of the **BLU-U®** will not be possible. Call for service.
	One or more fuses in the Fused Power Entry Module have blown.	Check the fuses in the Fused Power Entry Module, located next to the socket for the electrical cord on the base of the floor stand. • Turn the Key Switch and Main Power Switch to the "0" (off) position • Unplug the unit • With a small screwdriver, slide out the fuse holder • Check the status of the two fuses by using the fuse key. If either or both fuses are blown (as indicated by a break in the thin wire connecting the two metal ends of the fuse), replace with 5A fuses (0.5 x 20 mm slo-blo, Bussman # GMC-5A or equivalent). • Reinsert the fuse holder • Plug the unit into a standard 120 ~ wall outlet • Turn the **Main Power Switch** and **Key Switch** to the "**I**" (on) position.

Symptom	Possible Cause	What To Do
		If normal operation does not resume or the fuse continues to blow, there is an internal electrical fault. In this case use of the **BLU-U®** will not be possible. Call for service.
	Internal electrical fault.	Use of the **BLU-U®** will not be possible. Call for service.
System Status Indicator does not flash three (3) times when the *Start/Stop* button on the **Timer** is pressed	Neon light or control circuitry is not functioning properly.	Discontinue use of the **BLU-U®**. Call for service.
System Status Indicator rapidly flashing *Tubes not lit*	Control circuitry is not functioning properly.	Use of the **BLU-U®** will not be possible. Call for service.
System Status Indicator slowly flashing *Tubes lit*	Power output is above specified range.	Discontinue use of the **BLU-U®**. Call for service
	Control circuitry is not functioning properly.	Discontinue use of the **BLU-U®**. Call for service.
System Status Indicator on steady or intermittently *Tubes lit*	Power below specified range.	Complete treatment of patients. Call for service.
Tubes not all lit	Tube(s) cracked or broken.	Discontinue use of the **BLU-U®**. Call for service.
	Control circuitry is not functioning properly.	Discontinue use of the **BLU-U®**. Call for service.
F001 Error Code Displayed on **Timer**	**Timer** error	With the **Key Switch** turned to "**I**" (on), press the *Start/Stop* button to clear the **Timer** display.
F101 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.
F002 Error Code Displayed on **Timer**	**Timer** error	With the **Key Switch** turned to "**I**" (on), press the *Start/Stop* button to clear the **Timer** display.
F202 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.
F303 Error Code Displayed on **Timer**	**Timer** error	Call customer service to receive further instructions.

Transport and Storage:

1. The **BLU-U®** can be safely stored in a cool dry area. Care should be taken to avoid rough handling or jarring of the unit.

2. **Storage Conditions:**
   - -20°C to 60°C
   - 0 to 95% RH, Non-Condensing
   - 500hPa to 1600hPa

Cleaning/Disinfecting:

WARNING:
Turn the power off and disconnect the power cord before cleaning the machine. Failure to do so may result in severe electrical shock or death.
CAUTION:
Never immerse machine in liquids. Do not use abrasive materials to clean the machine. Do not allow water to enter this device. Do not clean the inside of this device. Doing so will cause damage to this machine.

1. The exterior surface of the **BLU-U®** may be wiped down with a mild disinfectant or isopropyl alcohol. Dry with a clean dry cloth.

2. The outside surface of the plastic shield may be wiped down with a mild disinfectant or isopropyl alcohol. Dry with a clean dry cloth.

3. If goggles are used for eye protection, their surface may be wiped down with a mild disinfectant or isopropyl alcohol after each use. Dry with a clean dry cloth.

Customer Service:

For service, repair, or calibration of this equipment call:

DUSA Pharmaceuticals, Inc.®
Phone: 1-877-533-3872

or

978-657-7500

Warranty Coverage and Disclaimers:

See the Terms and Conditions of your contract for specific information.

Manufactured For:
DUSA Pharmaceuticals, Inc.®
25 Upton Drive
Wilmington, MA 01887
www.dusapharma.com

JURAT

State/Commonwealth of TEXAS)
)
☐ City ☑ County of Dallas)

On 08/10/2021 (*Date*), before me, K L Hendrix (*Notary Name*),
the foregoing instrument was subscribed and sworn (or affirmed) before me by:

Duncan Hall
Name of Affiant(s)

❑ Personally known to me **-- OR --**

❑ Proved to me on the basis of the oath of _____ (*Name of Credible Witness*) **-- OR --**

☑ Proved to me on the basis of satisfactory evidence: driver_license (*Type of ID Presented*)

WITNESS my hand and official seal.

NOTARY PUBLIC STATE OF TEXAS
K L Hendrix
ID NUMBER
124579991
COMMISSION EXPIRES
December 14, 2024

Notary Public Signature: _____

Notary Name: K L Hendrix

Notary Commission Number: 124579991

Notary Commission Expires: 12/14/2024

Notarized online using audio-video communication

DESCRIPTION OF ATTACHED DOCUMENT

Title or Type of Document: Affidavit of Duncan Hall

Document Date: _____

Number of Pages (including notarial certificate): 90