CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

FINAL PRINTED LABELING

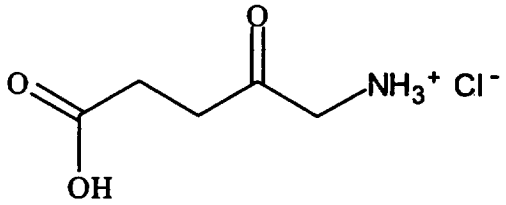
LEVULAN®KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%
For Topical Use Only
Not for Ophthalmic Use

DESCRIPTION

LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%, contains the hydrochloride salt of 5-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/cm^2, 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/cm^2. 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, non-hyperkeratotic, 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 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 hyperkeratotic actinic keratoses), 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 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. Lesion 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%)

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.

APPEARS THIS WAY
ON ORIGINAL

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.