PRODUCT MONOGRAPH

Levulan® Kerastick®

Aminolevulinic acid hydrochloride, 20% w/v
powder for topical solution

Photodynamic Therapy Photosensitizer

Manufactured By:
DUSA Pharmaceuticals, Inc., a Sun Pharma company
29 Dunham Road
Billerica, MA 01821
USA

Imported and Distributed By:
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Date of Preparation: May 06, 2004
Date of Revision: March 1, 2022

Product Monograph

PRODUCT NAME

Levulan® Kerastick®
aminolevulinic acid hydrochloride, 20% w/v
powder for topical solution

THERAPEUTIC CLASSIFICATION

Photodynamic Therapy Photosensitizer

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Aminolevulinic acid (ALA) is an endogenous compound, which is a metabolic precursor to protoporphyrin IX (PpIX), an intermediate precursor of heme synthesis. The rate of synthesis of PpIX is determined by the rate of synthesis of ALA, which in turn is regulated via a feedback control mechanism governed by the concentration of free heme. The administration of excess exogenous ALA bypasses the feedback control, and thus induces the intracellular accumulation of photosensitizing concentrations of PpIX in certain types of cells and tissues lining surfaces (epidermis, conjunctiva, oral mucosa, etc.).

Elevated endogenous levels of ALA, PpIX and other intermediates of porphyrin metabolism are due to enzymatic defects and characterize a group of well known metabolic diseases called Porphyrias.

Topical application of ALA to dysplastic, neoplastic, non-malignant inflammatory and hyperproliferative skin lesions such as Actinic Keratosis (AK), results in conversion of ALA to photosensitizing concentrations of PpIX. When such lesions are exposed to light of appropriate wavelength and energy, accumulated PpIX produces a photodynamic reaction, during which cytotoxic reactive oxygen species such as superoxide anions and hydroxyl radicals are formed. Biological membranes, particularly in mitochondria are sensitive to these oxygen radicals.

Selective photosensitization of AK lesions treated with ALA plus blue light irradiation (417 nm) is the basis of Levulan Photodynamic Therapy.

Pharmacokinetics

ALA molecule does not exhibit fluorescence, while PpIX has a high fluorescence yield. Time-dependent changes in surface PpIX fluorescence have been used to determine PpIX accumulation and clearance in AK lesions and perilesional skin. The mean clearance half-life of fluorescence for lesions was 30 ± 10 h and 28 ± 6 h for perilesional skin. Peak fluorescence intensity was reached in 11±1 h in AK's and 12±1 h in perilesional skin. The mean half-life of fluorescence for lesion was 30±10 h and 28±6 h for perilesional skin.

The estimated quantity of Levulan that will be topically applied for the treatment of AK lesions (7.15-15 mg) per patient, represents about 3.5% of the estimated 358 mg of ALA that is synthesized by the human body daily to support heme production.

INDICATIONS

Levulan Kerastick (aminolevulinic acid hydrochloride), with blue light irradiation, is indicated for the treatment of single and multiple non-hyperkeratotic actinic keratoses of the face and scalp.

CONTRAINDICATIONS

Levulan Kerastick (aminolevulinic acid hydrochloride) is contraindicated in patients with porphyria or in patients with known allergies to porphyrins, and in patients with known sensitivity to any of the components.

WARNINGS

Levulan Kerastick (aminolevulinic acid hydrochloride) contains alcohol and should not be applied to eyes and on mucosal membranes.

Transient episodes of amnesia have been reported with Levulan Kerastick in combination with photodynamic therapy (PDT). Inform patients and their caregivers that Levulan Kerastick in combination with PDT may cause transient amnestic episodes. Advise patients to contact their healthcare provider if they develop memory impairment, confusion, or disorientation after treatment.

PRECAUTIONS

General

During the time period between the application of Levulan Kerastick and exposure to activating blue light, AK lesions will become photosensitive. Therefore, during that period patients should avoid exposure of the treated AK lesions to sunlight or any bright indoor light, *e.g.*, examination lamps, operating room lamps, or unshaded light bulbs at close proximity. Exposure to light may result in a burning or stinging sensation and cause erythema and edema of the lesions. Protective clothing/hat should be worn when outside. UV sunscreens will not protect against photosensitivity reactions caused by visible light.

Application of Levulan Kerastick to perilesional areas of photodamaged skin of the face or scalp will result in photosensitization of that area upon exposure to activating blue light, therefore, Levulan Kerastick should only be applied to individual actinic keratoses and only by a qualified health professional.

Drug Interactions

There have been no formal studies of the interaction of Levulan Kerastick 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 another known photosensitizing agent or use of Levulan Kerastick at the time period when the other photosensitizing agent has not been cleared from the body, might lead to an increase in the photosensitivity reactions of AKs treated with Levulan Kerastick. The following are the possible drugs which could lead to such increased reaction: griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines.

Pregnancy

It is not known whether Levulan can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Levulan should not be used in pregnant women unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risks to the fetus.

Pregnancy outcomes were examined in a retrospective study of patients with Erythropoietic Protoporphyria (EPP), who chronically overproduce protoporphyrin IX (PpIX), and of patients with Acute Intermittent Porphyria (AIP), who chronically overproduce ALA and porphobilinogen (DUSA Pharmaceuticals, 1998). Of 55 offspring of AIP patients evaluated, none was reported to have a congenital defect. Of 71 offspring born to the EPP patients in this study, 5 were reported to have congenital defects. One child was born with severe oxygen deprivation as the result of a maternal septate uterus. The other congenital defects consisted of one strawberry hemangioma, one umbilical hernia, one mild case of hypospadias, and one case of mitral valve prolapse. The congenital defects observed are very common. In addition, these defects were mild, and generally resolved without intervention.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, nursing should be discontinued for a period of 30 hours and milk from that period should be discarded.

ADVERSE REACTIONS

Moderate to severe stinging/burning were reported by 90% of patients during treatment with Levulan Kerastick and blue light treatment in Phase III trials. Less than 3% of patients discontinued light treatment due to stinging/burning. When AK lesions were retreated after 8 weeks the severity of stinging/burning was less with the second treatment. Prior to the application of Levulan Kerastick the incidence of erythema and edema of lesions was 76% and 1%, respectively. After light treatment the incidence of erythema rose to 99% and edema to 35%. Four weeks after light treatment the incidence of both erythema and edema returned to pretreatment values or improved.

Other localized cutaneous responses to Levulan PDT were a) crusting, observed in 49% of patients and 34% of lesions; b) itching, which was experienced by 30% of patients in 22% of lesions; and c) scaling, observed in 31% of patients and 19% of lesions. Erosion was reported in one study in 15% of the patients and 7% of the lesions; ulceration was reported in 5% or less of patients in each study. Wheal/flare was reported in 7% of patients.

Pigmentary changes of lesions, classified as hyper- or hypo-pigmentation, were uncommonly seen in the Phase III studies. For the pooled studies, 94% and 95% of AKs treated with Levulan Kerastick plus blue light had no pigmentary changes at weeks 8 and 12, respectively. At week 8, 5% of treated lesions were judged hyperpigmented and 1% hypopigmented. At week 12, 3% and 2% of lesions were deemed hyperpigmented and hypopigmented, respectively. Pooled data for AKs receiving vehicle plus blue light showed pigmentary changes in 12% of lesions at week 8, and 10% of lesions at week 12. Levulan PDT using blue light, therefore, does not reappear to promote pigmentary changes in AKs.

All related adverse experiences reported by $\geq$ 1% of patients treated with Levulan Kerastick plus blue light or Vehicle plus blue light in the two Phase III trials are pooled and summarized below.

No treatment-emergent, clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

Related Adverse Events[1] Reported in >1% of Patients in Phase III Studies

		Levulan	Vehicle
	No. Patients	181	62
Skin & Appendages	Carcinoma Skin	2.8%	3.2%
	Rash	1.7%	1.6%
	Skin Hypertrophy	1.7%	0.0%
	Herpes Simplex	1.1%	0.0%
	Skin Disorder	1.1%	0.0%
	Maculopapular Rash	1.1%	0.0%
	Seborrhea	0.0%	1.6%
	Acne	0.0%	1.6%

[1]If a patient experienced more than 1 episode for an adverse event, the patient was counted only once for that event.

Post-Market Adverse Drug Reactions

Nervous system disorders: transient amnestic episodes

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage does not apply to topical usage of the Levulan Kerastick (aminolevulinic acid hydrochloride). In the unlikely event that the drug is ingested, standard procedures for poisoning should be followed. In the event of accidental ingestion, the patient should be advised to avoid incidental exposure to direct light sources.

There is no information on overdose of blue light following Levulan Kerastick application.

DOSAGE AND ADMINISTRATION

Photodynamic therapy for actinic keratoses (AKs) with Levulan Kerastick (aminolevulinic acid hydrochloride) is a two-stage process involving photosensitization of the target lesions with the Levulan Kerastick, followed by irradiation with blue light. Application of Levulan must be done by a qualified health professional, and should take place 14-18 hours prior to scheduled light treatment. Administration of Levulan should be limited to the target lesion itself, and peri-lesional areas should be avoided. Lesions that have been treated with Levulan should not be washed until prior to the application of blue light.

Treated lesions that have not completely resolved after 8 or more weeks may be retreated with topical Levulan Photodynamic Therapy.

Treatment Timelines

DAY 1 – Levulan Application	DAY 2 – Blue Light Application
5 pm	7 am to 9 am
6 pm	8 am to 10 am
7 pm	9 am to 11am

Levulan Kerastick Application

Actinic keratoses targeted for treatment should be clean and dry prior to application of Levulan Kerastick. The Levulan Kerastick can be prepared either manually, or using the optional Kerastick Krusher. These methods are illustrated below:

Manual Preparation:

(1) Hold the LEVULAN KERASTICK so that the applicator tip is pointing up.



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



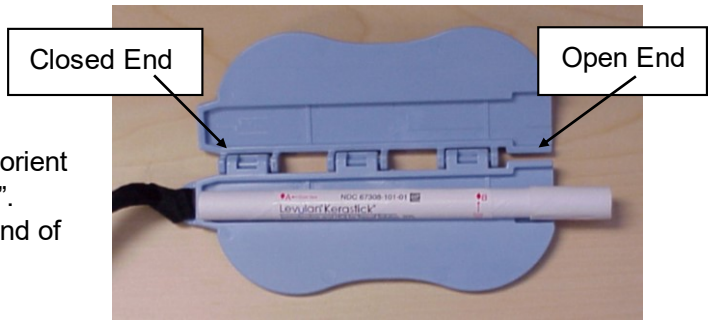
(3) Crush the top ampule containing the ALA HCl powder by applying finger pressure to Position B on the cardboard sleeve. To ensure both ampules are crushed continue crushing the applicator downward, applying finger pressure to Position A.



(4) Holding the LEVULAN KERASTICK between the thumb and forefinger, point the applicator away from the face, shake the LEVULAN KERASTICK gently for at least 30 Seconds to completely dissolve the drug powder in the solution vehicle. Do not press on the end cap while shaking.



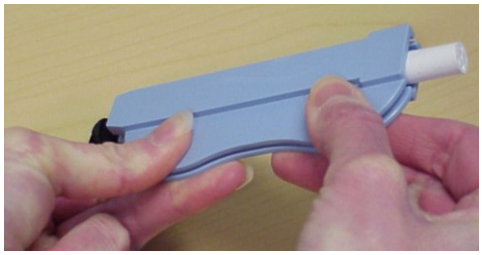
Optional Kerastick Krusher Preparation:



(1) Open the Kerastick Krusher and properly position one LEVULAN KERASTICK into the Krusher making sure to orient the LEVULAN KERASTICK label “A” with the Krusher “A”. Firmly seat LEVULAN KERASTICK against the closed end of the Krusher (cap should be at open end).



(2) Once positioned properly, close and firmly press the top and bottom handles together until the top and bottom handles touch one another along their length. A distinct crushing sound is made during this process. Ensure Krusher handles meet.



(3) Remove the LEVULAN KERASTICK from the Krusher.



(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 30 Seconds to completely dissolve the drug powder in the solution vehicle. Do not press on the end cap while shaking.



Following solution admixture, the dry applicator tip should be dabbed on a gauze pad until it is uniformly wet with solution. 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, without excess running or dripping. Once the initial application has dried, apply again in the same manner. The Levulan Kerastick must be used immediately following activation. If the solution application is not completed within 2 hours of activation, the applicator should be discarded and a new Levulan Kerastick used.

Formation of protoporphyrin IX and photosensitization of the treated lesions will take place over the next 14-18 hours. The patient should be advised to wear a wide brimmed hat or other protective apparel to shade the treated AK lesions from direct sunlight or other bright light sources until the scheduled light treatment has occurred.

If for any reason the patient cannot be given blue light treatment during the prescribed time after Levulan Kerastick application, he or she should avoid sunlight or direct indoor light for 30-48 hours to prevent the signs and symptoms of photosensitization.

Administration of Blue Light

Prior to light irradiation, the AKs to be treated should be gently rinsed off with water and patted dry. Photoactivation of Levulan-treated AKs is accomplished with blue light irradiation (417 nm). A 1000 second (16 minutes 40 seconds) exposure delivered at a power density of 10 mW/cm^2 is required to provide a 10 J/cm^2 light dose (this can be achieved using DUSA-4170 Blue Light Photodynamic Illuminator, or other similar licensed devices). Patients should be provided with blue-blocking yellow goggles to minimize ocular exposure to blue light during light treatment. Please refer to the operation instructions of the blue light device. Patients should be advised that they might experience transient burning and/or stinging at the target lesion sites during the period of light exposure.

If the blue light treatment 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 direct sunlight or excessively bright light.

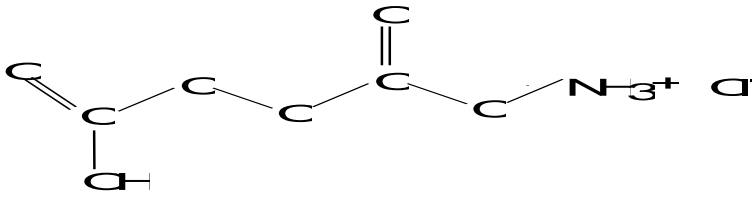
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: aminolevulinic acid hydrochloride

Chemical Name: 5-amino-4-oxopentanoic acid hydrochloride

Structural Formula:



Molecular Formula: $C_5H_9NO_3HCl$

Molecular Weight: 167.59

Description: aminolevulinic acid hydrochloride 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. Physical characteristics of aminolevulinic acid hydrochloride include a melting point range of 151 – 156 ºC (decomposition), a pH value of 1.77 for 1:5 aqueous solution, and a pKa value of 3.816.

Composition

The Levulan Kerastick applicator is a two component system in which the topical solution is admixed to produce a 20% solution just prior to use. One ampoule contains 1.5mL of solution vehicle comprised of alcohol USP (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampoule contains 354 mg of aminolevulinic acid hydrochloride.

Stability and Storage Recommendations

Store at controlled room temperature conditions 15-30 ºC (59-86 ºF). When exposed to light the Levulan Kerastick (aminolevulinic acid hydrochloride) active drug product may appear off-white; however, the strength, quality and purity of the material is unaffected by UV irradiation.

The Levulan Kerastick must be used immediately following activation. If the solution application is not completed within 2 hours of activation, the applicator should be discarded and a new Levulan Kerastick used.

Reconstituted Solutions

The Levulan Kerastick applicator is a two-component system in which the topical solution is admixed to produce a 20% solution just prior to the time of use. The applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. The Levulan Kerastick is activated by mixing the contents of the two ampoules (see **Dosage and Administration: Levulan Kerastick Application**). One ampoule contains 1.5 mL of solution vehicle comprised of alcohol USP (ethanol content – 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampoule contains 354 mg of Levulan.

AVAILABILITY OF DOSAGE FORMS

The Levulan Kerastick 20% topical solution, is a single-unit dosage form, supplied in a pack of 6. Each Levulan Kerastick applicator consists of a plastic tube containing two sealed glass ampoules and an applicator tip. One ampoule contains 1.5 mL of solution vehicle. The other ampoule contains 354 mg of Levulan (aminolevulinic acid hydrochloride). The applicator tube is covered with a protective cardboard sleeve.

INFORMATION FOR THE PATIENT

Levulan Kerastick
Clarion Medical Technologies Inc.
Photodynamic Therapy for Actinic Keratoses

Levulan Kerastick is a prescription topical solution used in combination with blue light (Photodynamic Therapy) for multiple actinic keratoses (AKs). When Levulan is applied to the skin, it accumulates in lesion cells. Cells that have accumulated Levulan become sensitive to light. This light sensitivity means that lesion cells containing Levulan are destroyed when they are exposed to light.

After Levulan Kerastick is applied to the AKs on your face or scalp in your doctor's office, the AKs will become sensitive to bright light (photosensitive). Care should be taken to keep the treated AKs dry and out of direct bright light. Fourteen to eighteen hours after application of Levulan Kerastick you will return to your doctor's office to receive light therapy.

Treatment Timelines

DAY 1 – Levulan Application	DAY 2 – Blue Light Application
5 pm	7 am to 9 am
6 pm	8 am to 10 am
7 pm	9 am to 11am

Prior to light therapy, your AKs will be rinsed with tap water. You will be given goggles to wear as eye protection during the light therapy. The light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, you may experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort, if any, will go away at the end of the light treatment. Following treatment, the AKs will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment. Temporary memory problems have happened during treatment with Levulan Kerastick in combination with light therapy. Contact your healthcare professional right away if you develop any problems with memory, confusion, or disorientation during treatment.

Photosensitivity

After Levulan Kerastick is applied to your AKs in your doctor's office, you should avoid exposure of the photosensitive AKs to direct sunlight or bright indoor light, *e.g.*, from examination lamps, operating room lamps, or unshaded light bulbs at close proximity, during the period prior to light therapy. Before going into bright sunlight, you should protect treated lesions from the sun by wearing a hat or similar head covering of light-opaque material. Ultraviolet light sunscreens will not protect you against photosensitivity reactions.

If for any reason you cannot return to your doctor for light therapy during the prescribed period after Levulan Kerastick application (14 to 18 hours), you should continue to avoid exposure of the photosensitized lesions to sunlight or excessively bright light for 30-48 hours and contact your doctor.

PHARMACOLOGY

Clinical Studies

ALA plus blue light has been used to treat multiple AKs of face and scalp in 406 patients in six clinical trials. Dose ranging studies (of the drug and of the light) have established that 20% Levulan Kerastick solution followed by treatment with blue light (417 nm) for a 1000 second dose of 10 J/cm^2 delivered at a power density of 10mW/cm^2 is the most effective treatment regime. Two identical randomized multi-center Phase III studies compared a total of 243 (181 ALA vs. 62 vehicle) patients with a total of 1909 face or scalp lesions. Compared to vehicle, response rates were significantly better ($p<0.001$) for ALA 8 weeks after the initial treatment (83%) and 4 weeks after re-treatment (91%). A total of 10/243 (4%) of patients prematurely withdrew or were discontinued from the pivotal trials. None of these patients withdrew due to study-related adverse events.

Summary of Phase III Studies

	ALA	Vehicle
N° of patients enrolled	181	62
Complete response in ≥ 75% of lesions at week 8	77 %	18 %
Complete response in ≥ 75% of lesions at week 12[1]	89 %	13 %
N° of lesions studied	1403	506
Complete response rate at week 8	83 %	31 %
Complete response rate at week 12[1]	91 %	25 %

[1]Lesions not exhibiting a complete response at Week 8 were retreated.

Response rates were analyzed for gender, age, and lesion location, as presented below.

Sub-group Response Rates

	≥ 75% AK clearing at week 8	≥ 75% AK clearing at week 12
Gender		
Male	99/134 (74)	106/121 (88)
Female	29/32 (91)	27/28 (96)
Age		
<65 years	48/58 (83)	46/47 (98)
≥65 years	80/108 (74)	87/102 (85)
Lesion Location		
Face	106/128 (83)	108/116 (93)

Scalp	22/38 (58)	25/33 (76)

For those lesions recorded as complete responses at Week 8, there was a recurrence rate of 9% with Levulan compared to 33% with Vehicle.

TOXICOLOGY

The estimated quantity of aminolevulinic acid hydrochloride that will be topically applied for the treatment of actinic keratosis lesions, 7.5 to 15 mg per patient, represents about 3.5% of the estimated 358 mg of aminolevulinic acid (ALA) per day that is synthesized by the human body to support heme production. In addition, the *in vivo* pharmacological and toxicological effects that may be associated with elevated systemic levels of ALA, Protoporphyrin IX (PpIX), and other intermediates of porphyrin biosynthesis in humans are well known, and characterize a group of metabolic diseases known as the porphyrias.

Due to the porphyrias, aminolevulinic acid (ALA) PDT is one of the few drug uses for which chronic (lifetime) human toxicology information is available. Data from a retrospective study suggest that a lifelong exposure to high systemic quantities of circulating ALA or PpIX does not predispose toward the development of cancer, and is not significantly genotoxic to the offspring of parents exposed to high circulating levels of these metabolites. Moreover, while there has been considerable interest in the association between elevated ALA levels and the neurological symptoms of acute intermittent porphyria, numerous attempts to clarify the relationship have yielded inconsistent results and contradictory conclusions. No consensus has been reached regarding the potential of ALA or other porphyrin intermediates to induce neurological effects at high systemic levels for extended periods of time. The low drug dose and single dose application used for topical ALA PDT are highly unlikely to result in neurological or other systemic toxicological findings.

Acute Toxicity

In acute toxicity studies, a single intravenous dose of up to 300 mg/kg aminolevulinic acid hydrochloride to male and female rats or mice resulted in no adverse effects. In male and female beagle dogs administered up to 100 mg/kg as a single intravenous dose, excessive salivation and vomiting was observed. Transient elevations in aspartate aminotransferase and alanine aminotransferase were observed following intravenous dosing. Vomiting was also observed in a pharmacokinetic study in beagles after single oral (gavage) and intravenous doses of 11 mg/kg.

In acute dermal toxicity studies in rats, the subcutaneous administration of aminolevulinic acid hydrochloride up to 1000 mg/kg did not result in any signs of toxicity with the exception of irritation and/or lesions present at the sites of injection. In acute dermal toxicity studies in rabbits, a single application of 10 – 30% aminolevulinic acid hydrochloride resulted in slight to moderate dermal irritation with placebo and active formulations; the level of dermal irritation was slightly higher in animals receiving the higher aminolevulinic acid hydrochloride doses.

Four acute studies in rats or mice were conducted to evaluate the toxicology of pyrazine 2, 5-dipropionic acid, the principal degradation product of aminolevulinic acid hydrochloride in aqueous solutions. Based on an estimated aminolevulinic acid hydrochloride dose of 7.5 – 15 mg per patient, the maximum per patient exposure to pyrazine 2, 5-diprpionic acid would be 0.0375 µg. Estimated LD_{50} values for oral and intraperitoneal pyrazine 2, 5-dipropionic acid in rats are greater than 5000 mg/kg and 1000 mg/kg, respectively, the highest doses evaluated by these routes of administration.

Carcinogenesis, Genotoxicity

No long-term carcinogenicity testing has been carried out using ALA.

Mutagenicity Studies

No evidence of mutagenic effects of ALA was seen in the four mutagenicity studies. In the *Salmonella-Escherichia coli/*Mammalian Microsome Reverse Mutation Assay (Ames mutagenicity assay), no positive increases 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 a positive increase in the number of revertants per plate of any of the tester strains in the presence of two light radiation doses, or in the absence of directed solar light radiation. In the L5178Y TK+/-Mouse Lymphoma Forward Mutation Assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. In the *in vivo* Mouse Micronucleus Assay, ALA was considered negative under the study exposure conditions.

REFERENCES AND SELECTED BIBLIOGRAPHY

DUSA Pharmaceuticals Inc. A retrospective study of clinical history in patients with Erythropoietic Protoporphyria (EPP) and in patients with Acute Intermittent Porphyria (AIP). Unpublished report; 1998.

Jeffes EW, McCullough JL, Weinstein GD, *et al*. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. Arch Dermatol 1997;133:727-32.

Kennedy JC, Pottier RH, Prosss DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B 1990;6:143-8.

Kennedy JC, Pottier RH. Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy. J Photochem Photobiol B 1992;14:275-92.

Kennedy JC, Marcus SL, Pottier RH. Photodynamic Therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. J Clin Laser Med Surg 1996;14:289-304.

Webber J, Kessel D, Fromm D. Side effects and photosensitization of human tissues after aminolevulinic acid. J Surg Res. 1997;68:31-7.

Webber J; Kessel D; Fromm D. On-line fluorescence of human tissues after oral administration of 5-aminolevulinic acid. J Photochem Photobiol B. 1997;38:209-14.

WebberJ; Kessel D; Fromm D. Plasma levels of protoporphyrin IX in humans after oral administration of 5-aminolevulinic acid. J Photochem Photobiol B 1997;27:151-3.