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APPLICATION NUMBER: 20-965

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 19 1998

Clinical Pharmacology/Biopharmaceutics Review (Addendum)

Aminolevulinic HCl, 20% Topical Solution	DUSA Pharmaceuticals Inc.
Levulan® Kerastick™	Valhlla, NY 10595
Reviewer: A. Noory	Submission Date:
NDA 20-965	June 29, 1998

Addendum

This document is an addendum to the review dated 5-Nov-98 and is addressing the pharmacokinetics and dosage and administration section of the package insert for Levulan® Kerastick™.

Comments for Labeling:

Under the "Pharmacokinetics" heading, replace the second and the third sentence with; The oral bioavailability of ALA was 50-60% with a mean Cmax of 4.65+/-0.94 µg/ml. Also in the same paragraph replace the fourth sentence with; The PpIX concentrations were low and were detectable only in 42% of the plasma samples.
Under the pharmacokinetics heading, after the third sentence insert the following two sentences: [redacted] Therefore Levulan should only be applied to the affected skin.

Under the "DOSAGE AND ADMINISTRATION" in the second sentence replace "14-18 hours" with [redacted]

/S/ 11/19/98

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CC: NDA 20-965 (ORIG),
HFD-540/DIV. File
HFD-540/Prj. Mjr./Cintron
HFD-880 (Noory)
HFD-880 (Bashaw)
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(CDR. Attn. B. Murphy)
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Clinical Pharmacology/Biopharmaceutics Review

Aminolevulinic HCl, 20% Topical Solution	DUSA Pharmaceuticals Inc.
Levulan® Kerastick™	Valhlla, NY 10595
Reviewer: A. Noory	Submission Date:
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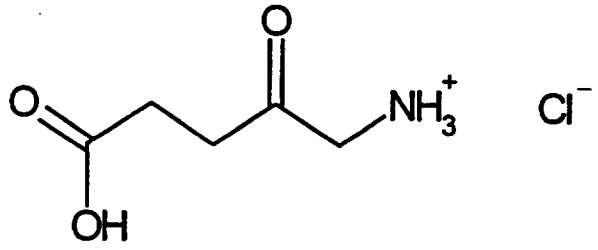
Review of an NDA

I. Background:

Levulan® Kerastick™ is a two component system applicator. The system (shown on Page 8 of the appendix), consists of two ampoules, one contains the vehicle solution and the other contains 354mg of Levulan® (aminolevulinic acid HCl). Levulan® is mixed with the vehicle solution to produce a 20% solution just before application by a health professional by crushing the ampule in the applicator. Levulan® photosensitizes actinic keratoses lesions (AK) by inducing the accumulation of protoporphyrin IX (PpIX) in cells and tissues for photodynamic therapy with the 4170 Blue Light Photodynamic Therapy Illminator (BLU-U™). As part of this NDA, the applicant has submitted the results of a pharmacokinetic study using both intravenous and oral dosing, a pharmacokinetic study using topical administration, and an in vitro Percutaneous absorption study. Aminolevulinic acid HCl is a white to off-white crystalline powder, highly soluble in water, sparingly soluble in ethanol and methanol, and insoluble in mineral oil or hexane with a molecular weight of 167.59. The chemical name of Aminolevulinic acid HCl is 5-amino-4-oxopentanoic acid hydrochloride with the following structural formula.



II. Recommendation:

In support of the human pharmacokinetic and bioavailability portion of this NDA the applicant submitted the result of three studies. These studies adequately characterized the pharmacokinetic and bioavailability of aminolevulinic acid from the Levulan® Kerastick™. From the biopharmaceutics point of view the NDA 20-965 is approvable.

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III. Overview of pharmacokinetic section/disease:

The human pharmacokinetic and bioavailability section of this NDA consists of three study reports:

1. Pharmacokinetics of 5-Aminolevulinic Acid (ALA) and protoporphyrin IX (PpIX) in healthy Volunteers after Intravenous and Oral Dosing, (PK-01)
2. Pharmacokinetics of Levulan Induced Protoporphyrin IX in Actinic Keratosis and Adjacent Skin, (Pharm-03)
3. In Vitro Percutaneous Absorption of [^{14}C]-Aminolevulinic Acid in Human Skin.

Chronic exposure to sunlight may increase the incidence of squamous and basal cell carcinoma of the skin in fair, white-skinned persons which is directly related to the amount of yearly sunlight to the exposed area. Precancerous keratotic lesions (actinic keratoses [AK]) are frequent consequences of many years of over-exposure. The keratoses are usually hard and sharp on palpation, and gray to dark in color. They differ from warty brown seborrheic keratoses, which increase in number and size with age but occur on covered as well as uncovered areas of the body and are not premalignant.

The accumulation of protoporphyrin IX (PpIX) in actinic keratoses and photosensitization of the lesion by light of a certain wavelength will result in necrosis of the lesion. Aminolevulinic Acid (ALA), an endogenous substance, is an intermediate in the biosynthesis of porphyrins, it induces the accumulation of PpIX. Attachment 9 of the appendix shows the pathway for the synthesis of PpIX.

Levulan® Kerastick™ will be applied by a health profetional to assure the proper amount and method of application. As mentioned previously the system consists of two ampoules, one contains the vehicle solution and the other contains 354mg of Levulan® (aminolevulinic acid HCl). The formulation of the vehicle solution is shown in page 10-11 of the appendix.

Analytical:

The analysis of PpIX in human plasma was carried out by [redacted] based on a method by Meyer and Vogt "Ion-Pair Reversed HPLC Determination of Porphyrins from Red Blood Cells" Chromotographia Vol. 16, P190. The assay was shown to be specific for PpIX and linear over a range of [redacted] ng/ml. The lower limit of quantitation [redacted] ng/ml. Representative chromatograms are included in the appendix, page 12. The analysis of ALA was based on a method by Okayama et al, Clin. Chem. 36:1494-1497, 1990. The

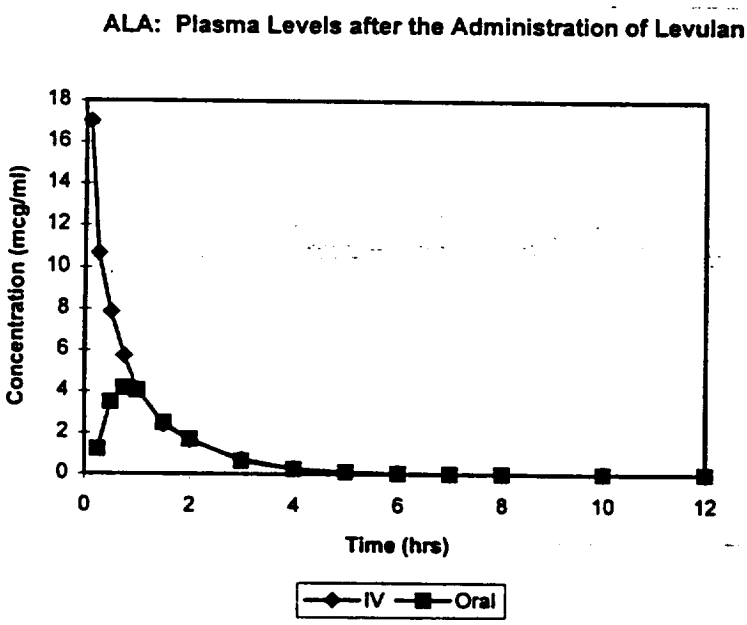
assay was shown to be specific for ALA and linear over a range of [redacted] µg/ml. The lower limit of quantitation [redacted] µg/ml. Representative chromatograms are included in the appendix, page 13.

Pharmacokinetic and Bioavailability: Study # PK-01

The objective of this study was to determine the bioavailability of 5-aminolevulinic acid.(ALA). Also the plasma concentrations of protoporphryin IX (PpIX) were measured. Six healthy male volunteers were enrolled in this crossover study. Each subject received an intravenous and an oral dose of 128mg of ALA HCl (equivalent to 100mg of ALA) with a washout period of 6-7 days. The solution for injection was also used for oral administration. The study design was a two-way crossover, and the trial is summarized in the appendix page 14-17. The table below shows the AUC and the C_{max} for ALA after Oral and the IV administration.

Pharmacokinetic Parameters for ALA; Mean ± SD; N=6		
PK-parameter	Intravenous	Oral
AUC (0-∞) µg*hr/ml	12.50 ± 2.89	7.30 ± 1.25
C_{max} µg/ml	15.44 ± 6.60	4.65 ± 0.94
% Bioavailability		60.3 ± 13.4

The mean plasma concentration-time curves for ALA are shown below.



Although the plasma concentration profile for the ALA was determined easily, the plasma concentration profile for the PpIX could not be determined at all. The PpIX concentrations were low and erratic. Following the intravenous and oral administration of ALA, the levels of PpIX was only detectable in 48% and 38% of the plasma samples respectively. The levels are shown on page 18 of the appendix. The results of this study demonstrate that the level of PpIX does not correspond to ALA administered. In fact, in one subject (# 4) the concentration of PpIX was similar or higher

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