CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

PHARMACOLOGY REVIEW(S)

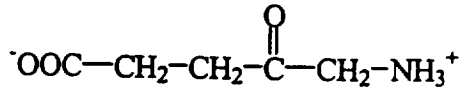
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: 5-aminolevulinic acid, ALA, photodynamic therapy, actinic keratoses
Reviewer Name: Amy Nostrandt
Division Name: Division of Dermatologic and Dental Drug Products
HFD# 540
NOV 19 1999
Review Completion Date: 11/19/1999

Review number: 2
IND/NDA number: NDA 20-965
Serial number/date/type of submission: resubmission (AZ), response to AE letter, received 10/4/1999
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Guidelines, Inc. for DUSA Pharmaceuticals, Inc.
Manufacturer for drug substance: [redacted]

Drug:

Code Name: 5-ALA HCl, 5-ALA, ALA
Generic Name: 5-aminolevulinic acid HCl
Trade Name: Levulan® (aminolevulinic acid HCl) Kerastick™ for topical solution 20%
Chemical Name: 5-amino-4-oxopentanoic acid
CAS Registry Number: not included in this submission
Molecular Formula/ Molecular Weight/Structure:
(5-aminolevulinate)
$C_5H_9NO_3$, MW = 131.13



Relevant INDs/NDAs/DMFs:
in HFD-150:
IND [redacted]
IND [redacted]
IND
IND

in HFD-540:
IND [redacted]
for topical photodynamic therapy of actinic keratosis
IND [redacted]
IND
IND
IND
IND

in HFD-580:
IND
IND

Drug Class: photodynamic therapy

Indication: for the treatment of actinic keratoses of the face and scalp

Clinical formulation: constituted Levulan® (5-ALA HCl)

Ingredient	"theoretical quantity" mg/ml
Levulan (5-ALA HCl)	
Alcohol, USP	
Purified water, USP	
Laureth-4	
Isopropyl alcohol, USP	
Polyethylene glycol	
Total	

Route of administration: An ampoule containing 5-ALA HCl in powder form is broken to allow admixture with the vehicle to form a 20% solution. The solution is immediately applied topically to the lesion only. After hours, the site is irradiated with the applicant's companion device, a blue light source with an emission peak of 417 nm and a bandwidth of nm.

Introduction and drug history: The current submission is a resubmission of an approvable NDA. The only changes that impact pharmacology and toxicology are in the label. Those changes are addressed below.

OVERALL SUMMARY AND EVALUATION:
Communication Review:

- **Labeling Review (NDA):**

1. Under "Carcinogenesis, Mutagenesis, Impairment of Fertility," all references to "5-ALA" were changed to read by the applicant. References to the drug substance, as opposed to the drug product, were changed to ALA HCl, as proposed by the chemistry reviewer. For descriptions of genotoxicity studies, which were conducted using a solution of 5-ALA in an acetate buffer, the wording should be changed back to read ALA.

2. The sentence, "PpIX formation was not demonstrated in the in vitro studies" should be moved to a position immediately after the descriptions of those studies and "the" should be changed to "these."

3. Other minor changes, such as more concise wording, case corrections, etc., are made below.

RECOMMENDATIONS:

The following sections should be revised as follows:

Carcinogenesis, Mutagenesis, Impairment to Fertility: No carcinogenicity testing has been carried out using [redacted]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), [redacted]ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence [redacted] or [redacted] absence of [redacted] simulated solar light. In the L5178Y TK+/- mouse lymphoma forward mutation assay, [redacted] 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, [redacted] ALA was considered negative under the study exposure conditions. [redacted] 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 [redacted]ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to [redacted] ALA HCl might have on fertility or reproductive function.

Pregnancy Category C: Animal reproduction studies have not been conducted with [redacted] 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 [redacted] Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

APPEARS THIS WAY
ON ORIGINAL

[redacted] /S/ 11/19/99

Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

cc:
NDA 20-965
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Okun
HFD-540/CHEM/Hathaway
HFD-540/PMS/Cintron
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Draft date (# of drafts): 11/19/99 (1)

Concurrence Only:
HFD-540/DD/WILKIN /S/ 11/21/99

HFD-540/TLPHARM/JACOBS /S/ 11/19/99

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