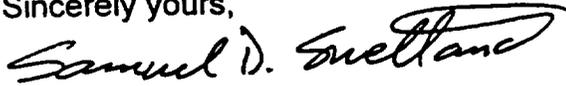


We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

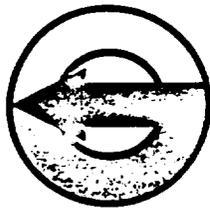
Sincerely yours,



Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSANDA Documents\Cover Letter-8.doc

APPEARS THIS WAY
ON ORIGINAL



GUIDELINES INCORPORATED

SUPPL NEW COURTES

DUPLICATE

September 30, 1998



Olga Cintron, Project Manager
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
2nd Floor North
9201 Corporate Boulevard
Rockville, MD 20850

REFERENCE: New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965

Dear Olga:

Attached please find copies of two correspondences submitted regarding the above application. This information was provided directly to the requesting parties as a result of a telephone correspondence. In each case, no new information has been provided that was not available in the original NDA submission. These correspondences are being provided to you for informational purposes and to maintain a record of the NDA correspondence. Please feel free to call me if you have any questions regarding either of these correspondences.

Sincerely yours,

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSAWDA Documents\Cover Letter-6.doc

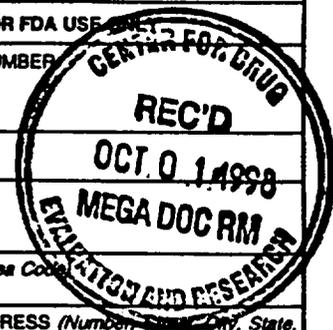
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER



APPLICANT INFORMATION

NAME OF APPLICANT DUSA Pharmaceuticals, Inc.	DATE OF SUBMISSION September 30, 1998
TELEPHONE NO. (Include Area Code) (914) 747-4300	FACSIMILE (FAX) Number (Include Area Code) (914) 747-7563
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 400 Columbus Avenue Valhalla, NY 10595	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Guidelines, Inc. 10320 USA Today Way Miramar, FL 33025 (954) 433-7480 FAX: (954) 432-9015

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-965		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Aminolevulinic Acid HCl	PROPRIETARY NAME (trade name) IF ANY Levulan Kerastick TM	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 5-amino-4-oxopentanoic acid	CODE NAME (if any) 5-ALA HCl, 5-ALA, ALA	
DOSAGE FORM: Solution	STRENGTHS: 20%	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: Treatment of [redacted] actinic keratoses of the face and scalp		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
REASON FOR SUBMISSION General Correspondence
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment to Form FDA 356h

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment to Form FDA 356h



GUIDELINES INCORPORATED

September 30, 1998

Richard Felten, PhD
Division of General and Restorative Devices
Office of Device Evaluation
Center for Device and Radiological Health
Food and Drug Administration
HFZ-410, Room 310K
9200 Corporate Boulevard
Rockville, MD 20850

REFERENCE: DESK COPY –

New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965

Dear Dr. Felten:

On behalf of our client, DUSA Pharmaceuticals, Inc., and pursuant to our phone conversation yesterday regarding the above referenced NDA, attached please find additional copies of the following NDA volumes:

1. Volume 1.1.1
2. Volume 1.10.1
3. Volume 1.10.2

If you require any further information please feel free to call me.

Sincerely yours,

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

CC: NDA 20-965

SDS/sds
DUSA\NDA Documents\Cover Letter-7.doc



**GUIDELINES
INCORPORATED**

FAXED
9-18-98

September 18, 1998

Jose Carreras, MD
Division of Scientific Investigations (HFD-344)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 1, Room 125
7520 Standish Place
Rockville, MD 20855

**REFERENCE: New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965**

Dear Dr. Carreras:

On behalf of our client, DUSA Pharmaceuticals, Inc., and pursuant to our phone conversation yesterday regarding the above referenced NDA, attached please find the requested information as outlined below.

1. A list of the names and addresses of the clinical investigators who participated in the Phase III clinical trials (Protocols ALA-018 and ALA-019).
2. The number of patients enrolled in each center (Protocols ALA-018 and ALA-019) by treatment arm.
3. A list of all serious adverse reactions for Protocols ALA-018 and ALA-019.

Please note that the page numbers on the bottom right corner of each page reference the location of this data in the original NDA submission. If you require any further information please feel free to call me.

Sincerely yours,

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSA/WDA Documents/Cover Letter-5.doc

Protocol ALA-018

TABLE 6.1
List of Principal investigators

Principal Investigator	Address
Mary Gail Mercurio, MD	Department of Dermatology Clinical Pharmacology Unit Columbia Presbyterian Medical Center 161 Fort Washington Ave. Room 750 New York, NY 10032
Scott D. Glazer, MD	
Mark Ling, MD	Director, Clinical Pharmacology Unit Emory University Hospital 1364 Clifton Rd., Room 640B Atlanta, GA 30322
Daniel J. Piacquadio, MD	
J. Richard Taylor, MD	VA Medical Center Dermatology Service 1201 N. 16 th Street Miami, FL 33125
S. Elizabeth Whitmore, MD	Johns Hopkins University Department Dermatology 550 Building, Suite 1002 550 N. Broadway Baltimore, MD 21205
John Goodman, MD	Hill Top Research, Ltd. 900 Osceola Drive West Palm Beach, FL 33409
Harold Farber, MD	Hill Top Research Ltd. Einstein Center One 9880 Bustleton Ave., Suite 203 Philadelphia, PA 19115

b. Statistician:

c. Clinical Trial Supply Management:

- i. Guidelines, Inc. was responsible for the packaging, labeling and shipping of all clinical supplies used in this study.
- ii. A central laboratory [redacted] was used to analyze all hematology, chemistry and urine parameters. Instructions and supplies for handling the samples were provided to the investigators prior to study initiation. [redacted] analyzed the samples and the test results were to be reported to the investigator within 48 hours of receipt. Copies of laboratory

10. STUDY PATIENTS

10.1 Disposition of Patients.

A total of 117 patients were randomized to either Levulan or Vehicle. As may be seen, 88 patients received Levulan and 29 received Vehicle. The number of patients by center is presented in Table 10.1.1 and summary Table 1.1.

**Table 10.1.1
 Number of Patients Enrolled by Center**

Investigator	Levulan	Vehicle	Total
Glazer	18	6	24
Ling	18	6	24
Mercurio	4	0	4
Piacquadio	5	2	7
Taylor	15	5	20
Whitmore	8	2	10
Goodman	13	5	18
Farber	7	3	10
Total	88	29	117

As specified in the protocol, each patient had to have a minimum of 4 target lesions on the face or scalp for entry into the study. The number of lesions by center and treatment is presented in Table 10.1.2 and summary Table 1.2.

**Table 10.1.2
 Number of Lesions by Center**

Investigator	Levulan	Vehicle	Total
Glazer	104	39	143
Ling	109	30	139
Mercurio	19	0	19
Piacquadio	28	12	40
Taylor	166	57	223
Whitmore	58	20	78
Goodman	66	29	95
Farber	65	16	81
Total	615	203	818

The data are summarized in summary Table 41.2 and listed by patient in Patient Data Listing 19.

12.3 Deaths, Other Serious Adverse Events

12.3.1 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

There were no deaths reported during the study.

12.3.1.2 Other Serious Adverse Events

There was only one patient with a serious adverse event. Patient 18219 was hospitalized for an elective neurosurgical procedure for the treatment of a familial tremor refractory to medical therapy.

12.3.1.3 Other Significant Adverse Events

Two patients (18515 and 18517) had their light treatment terminated early due to discomfort.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Patient Number: 18515
Site/Investigator: # 5, Richard Taylor, MD
Reason for Narrative: Light treatment terminated
Protocol: ALA-018
Treatment Group: Levulan 20 %

Patient 18515 was first diagnosed with actinic keratoses (AK) in 1996 and had not received any treatment prior to coming on study.

At the Screening visit on 4/22/97, medical history was significant for hypertension (HTN), peptic ulcer disease (PUD), anemia, osteomyelitis with prior arthroplasty of the left knee, chronic obstructive pulmonary disease, cataract and diminished hearing, renal calculi and constipation. Physical examination and vitals were WNL and the patient was determined to have Type I skin. Medications included acetaminophen 500 mg, PRN (osteomyelitis), Doxazosin 8 mg, QHS (HTN), psyllium 1 tbs. after meals (prophylaxis constipation), simethicone 80 mg after meals (PUD) and sunscreen for sun protection. Serum creatinine was slightly elevated at baseline (1.6 Range (R): 0.5 – 1.5 meq/L) and judged not clinically significant. Other laboratory parameters were WNL.

**Table 6.1
 Principal Investigators**

Investigator	Address
Diana Chen, M.D.	Northwestern University Medical School Department of Dermatology 222 East Superior Avenue, 3rd Floor Chicago, IL 60611
Joseph Fowler, M.D.	Family and Occupational Dermatology 310 East Broadway, Suite 100 Louisville, KY 40202
Luciann Hruza, M.D.	Washington University School of Medicine 1040 North Mason Road, Suite 120 St. Louis, MO 63141
Tania Phillips, M.D.	Boston University Department of Dermatology 609 Albany Street, 4th Floor Boston, MA 02118
Tena Rallis, M.D.	University of Utah Department of Dermatology 50 North Medical Building Salt Lake City, UT 84132
David Tashjian, M.D.	Hilltop Research, Inc. 6079 North Fresno Street, Suite 101 Fresno, CA 93710
Charles Taylor, M.D.	Wellman Laboratories of Photomedicine Department of Dermatology, BHX-630 Massachusetts General Hospital 50 Blossom Street Boston, MA 02114
Gerald Weinstein, M.D.	University of California, Irvine Department of Dermatology Medical Sciences, I-C340 Irvine, CA 92717

Obligations for monitoring were shared by DUSA and [redacted]
 Obligations for data management, statistical analysis, and report writing were transferred to [redacted]. The following is a list of the organizations that were key with respect to the conduct of the clinical trial.

**APPEARS THIS WAY
 ON ORIGINAL**

10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

A total of 126 patients were randomized to have either Levulan or Vehicle applied. The number of patients randomized by each center is presented in the table below (Table 10.1.1). As shown in Table 10.1.2, 93 patients were randomized to receive Levulan, and 33 patients were randomized to receive Vehicle.

Table 10.1.1
Number of Patients Enrolled by Investigator

Investigator	Levulan	Vehicle	Total
Chen	8	4	12
Fowler	12	4	16
Hruza	15	5	20
Rallis	12	4	16
Phillips	12	4	16
Taylor	12	4	16
Weinstein	12	4	16
Tashjian	10	4	14
Total	93	33	126

Data Source: End-of-Text Table 1.1.

APPEARS THIS WAY
ON ORIGINAL

12.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

A listing of all adverse events, sorted by treatment group and investigator, are presented by patient in Patient Data Listing 13, which is located in Appendix 16.2.7 of this report. Both the verbatim and the coded COSTART term, as well as the day of onset, duration, intensity, relationship to study drug, and treatment required are presented.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 LISTING OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT EVENTS

12.3.1.1 Deaths

One patient (Pt. No. 19410) died during participation in the study. The relationship for the serious adverse events (jaundice, carcinoma of liver, liver failure, and hepatocellular carcinoma) were judged to be "remote." A patient narrative is presented in Section 12.3.2.

12.3.1.2 Other Serious Events

Five patients had other serious adverse events during the study. All were from the Levulan treatment group. The severity of these serious adverse events ranged from mild to severe with an outcome of "recovered" for all 5 patients. The relationship to study medication for these serious adverse events was judged to be "not related" for all five patients. These adverse events are presented in Table 12.3.1.2.1.

The patient narratives are presented in Section 12.3.2.

There were no serious adverse events reported during the study in the Vehicle treatment group.

**Table 12.3.1.2.1
 Serious Adverse Events**

Treatment Group	Investigator	Patient No.	Severity	Study Drug Relationship	Date of Onset ¹	Date of Onset ²	Adverse Event (COSTART/Verbatim Term)	Disc.
Levulan								
	Chen	19101	Severe	Not Related	3	-	Skin Carcinoma/ Basal Cell	No
	Fowler	19214	Moderate	Not Related	22	-	Skin Carcinoma/ SCC-Right Anterior Lower Leg	No
	Rallis	19410	Mild Life threatening	Remote Remote	37 55	-	Jaundice/ Jaundice Carcinoma of Liver/ Liver Failure/Hepatocellular Carcinoma	No
	Phillips	19511	Moderate Moderate	Not Related Not Related	14 27	-	Pneumonia/ Pneumonia Chest Pain/ Chest Pain	No
	Taylor	19613	Mild	Not Related	10	-	Accidental Injury/ Automobile Accident Pain & Bruising	No
	Tashjian	19802	Severe	Not Related	83	26	Bradycardia/ Bradycardia	No

Disc. = Discontinued from the study.
 • Relative to the day of initial treatment.
 • Relative to the day of retreatment Visit 5 (Week 8), if applicable.
 Data Source: End-of-Text Table 33; Patient Data Listing 13; and CRF page 41.

12.3.1.3 Other Significant Adverse Events

No patient discontinued from the study because of adverse events.

**APPEARS THIS WAY
 ON ORIGINAL**



**GUIDELINES
INCORPORATED**

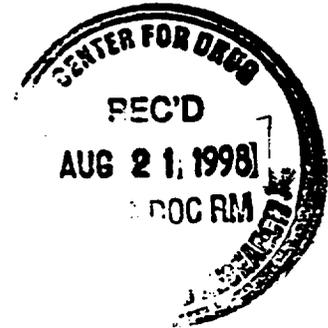
ORIG AMENDMENT
ORIGINAL
BC



FAXED
8/20/98

August 20, 1998

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852



REFERENCE: New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965

Dear Dr. Wilkin:

On behalf of our client, DUSA Pharmaceuticals, Inc., we herewith amend the subject application in accordance with 21CFR §314.60 to provide the following information requested by the Division during a telephone conversation on 20 August 1998.

As stated in the Device Manufacturing Documentation Section of the above referenced NDA (Section X. [redacted] the final inspection and QC Testing of the clinical devices was conducted by [redacted] on behalf of DUSA Pharmaceuticals, Inc. As indicated in our phone conversation, we confirm that the facilities and documentation to support the QC Testing of the clinical devices by [redacted] are ready for FDA inspection. This facility has not been inspected previously by FDA. [redacted] address is as follows:



Additionally, as pointed out during our phone conversation, DUSA Pharmaceuticals, Inc. is acquiring [redacted] However, this will not impact the availability of the site and documentation for inspection.

We trust that this information is satisfactory and that the application will be found acceptable for filing.

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

Sincerely yours,



Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSA\NDA Documents\Cover Letter-4.doc

**APPEARS THIS WAY
ON ORIGINAL**

design and manufacture of the clinical devices is available at [redacted] and is ready for FDA inspection.

We trust that this clarification is satisfactory and that the application will be found acceptable for filing.

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

Sincerely yours,



Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSAANDA Documents\Cover Letter-3.doc

APPEARS THIS WAY
ON ORIGINAL

DUSA

DUSA PHARMACEUTICALS, INC.

400 COLUMBUS AVENUE

VALHALLA, NY 10595

TEL 914.747.4300

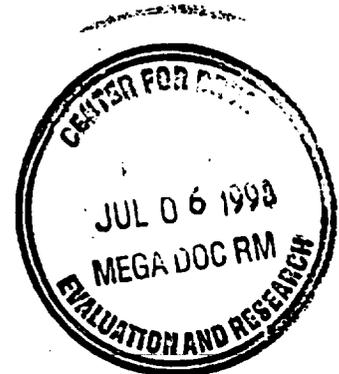
FAX 914.747.7563

WWW.DUSAPHARMA.COM



June 29, 1998

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852



REFERENCE: New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965

Dear Dr. Wilkin:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act, and in accordance with Title 21 of the Code of Federal Regulations, Section 314.50, DUSA Pharmaceuticals, Inc. herewith submits an original New Drug Application (NDA) for Levulan® (aminolevulinic acid HCl) Kerastick™ for Topical Solution, 20%, for use in the treatment of multiple actinic keratoses (AKs) of the face and scalp.

The Levulan Kerastick for Topical Solution, 20% contains Levulan®, the hydrochloride salt of aminolevulinic acid, a naturally occurring 5-carbon aminoketone. When applied topically, Levulan photosensitizes AKs for photodynamic therapy with the Model 4170 Blue Light Photodynamic Therapy Illuminator (Blu-U™).

The Levulan Kerastick is a two component applicator in which Levulan and Topical Solution Vehicle are admixed to produce a 20% w/v solution just prior to administration. The applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of a

hydroalcoholic solution vehicle (ethanol content = 48% v/v), comprised of alcohol, water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of Levulan drug substance. The applicator tube is covered with a protective cardboard sleeve.

The Levulan Kerastick and Blu-U Illuminator comprise a drug/device combination product which has been assigned to the administrative jurisdiction of the Center for Drug Evaluation and Research. Accordingly, information covering the design and manufacture of the illuminator is being provided within the NDA. At the request of the Center for Devices and Radiological Health, the NDA contains information on the Model 4170 illuminator, the blue light illuminator used in the Phase III clinical trials conducted by DUSA Pharmaceuticals. Information on the proposed commercial device, the Model 4170 Blu-U, will be included in an NDA Amendment to be submitted in February, 1999.

At the 4 November 1996 End of Phase II Meeting, the Chemistry Reviewer indicated that samples of the container closure system should be provided with the NDA since the Levulan Kerastick is a novel packaging configuration. Therefore, appended to this cover letter (Archival Copy and Chemistry Review Copy only) are samples of the finished dosage form as used in the Phase III clinical trials. Please note that these samples have been labeled for demonstration purposes only, and do not reflect proposed commercial labeling or previous clinical labeling.

At the 22 October 1997 Pre-NDA Meeting, the Division of Biometrics requested that the Phase III clinical data be submitted on computer disk, and instructions on the type and format of the data files were provided. Appended to this letter (Archival Copy and Statistical Review Copy only) are one set of disks containing the Phase III data formatted as requested, a listing of the data provided, and instructions for the extraction of the data from the zipped files.

A large number of photographs (as 35 mm slides) were taken to document the clinical findings of the Phase III trials. While these slides have not been submitted as part of the NDA, they are all available for review, and will be provided upon Agency request.

**APPEARS THIS WAY
ON ORIGINAL**

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

Sincerely yours,

DUSA PHARMACEUTICALS, INC.

A handwritten signature in black ink, appearing to read 'SLM', with a stylized flourish at the end.

Stuart L. Marcus, MD, PhD
Senior Vice President, Scientific Affairs
and Chief Scientific Officer

APPEARS THIS WAY
ON ORIGINAL

FORWARD PLANNING MEETING MINUTES

NDA 20-965 Levulan (aminolevulinic HCl) Kerastick for Topical Solution, 20%

Date: August 18, 1998.

Sponsor: DUSA Pharmaceuticals

Authorized Rep.: Guidelines, Inc.

Pharmacologic class: Photodynamic Therapy Photosensitizer

Type: 1S

Indication: Treatment of [redacted] actinic keratoses of the face and scalp

Active ingredient: aminolevulinic acid HCl

Filing Date: August 30, 1998.

Regulatory Due Date: December 28, 1998.

User Fee Due Date: May 1, 1999.

Attendees: Jonathan Wilkin, M.D., Division Director, HFD-540
Martin Okun, M.D., Medical Officer, HFD-540
Assadollah Noory, Pharmacokineticist, HFD-880
Dennis Bashaw, Pharm. D., Team Leader Biopharmaceutics, HFD-880
Amy Nostrandt, Ph.D., Pharmacologist, HFD-540
Norman See, Ph.D., Pharmacologist, HFD-540
Steve Hathaway, Ph.D., Chemist, HFD-830
Wilson DeCamp, Ph.D., Team Leader/Chemistry, HFD-830
R. Srinivasan, Ph.D., Team Leader/Biostatistics, HFD-725
Shahla Farr, M.S., Biostatistics, HFD-725
Richard Felten, Chemist, CDRH, HFZ-410
Mary Jean Kozma-Fornaro, Supv. Project Manager, HFD-540

Handwritten notes:
all in
for
11/23/98

Discussion:

The meeting was convened to determine the adequacy of NDA 20-965 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of general content and format requirements.

From a preliminary evaluation of the general content and format as well as the non clinical pharmacology and toxicology, human pharmacokinetics, clinical data, chemistry, statistical, and device sections of the application, it was recommended that NDA 20-965 be filed.

All disciplines stated that no additional information from the Sponsor is needed at this time with the exception of Devices. It was not clear if the commercial device manufacturing site was ready for inspection. During the meeting, the Sponsor was contacted to clarify statements regarding readiness for inspection of the manufacturing site of the commercial device. The Sponsor indicated that the [redacted] is ready for inspection. Details of this telephone conversation are attached.

Expected date of draft review:	Chemistry	12/98
	Pharmacology	2/99
	Biopharmaceutics	10/98
	Biostatistics	2/99
	Clinical	2/99

It was agreed that an action on this application should be issued by 5/99.

**APPEARS THIS WAY
ON ORIGINAL**

Attachments: Checklists, Memo of Telecon dated 8/18/98.

cc:

Original NDA 20-965

HFD-540/DIV FILE

HFD-540/CHEM/Hathaway

HFD-540/SR CHEM/DeCamp

HFD-540/PHARM/Nostrandt

HFD-540/SR PHARM/Jacobs

HFD-725/BIOSTAT/Farr

HFD-725/SR BIOSTAT/Srinivasan

HFD-540/MO/Okun

HFD-880/PK/Noory

HFD-880/SR BIOPHARM/Bashaw

HFD-540/SUPV PROJ MGR/Kozma-Fornaro

HFD-540/PROJ MGR/Cintron

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: August 18, 1998
NDA: 20-965
DRUG: Levulan (aminolevulinic HCl) Kerastick for Topical Solution, 20%
SPONSOR: Guidelines Incorporated
Sam Swetland
Dr. Alan Gollup
FDA: Dr. Jonathan Wilkin, DD, HFD-540
Mr. Richard Felten, Reviewer, CDRH
Mary Jean Kozma-Fornaro, C, PMS, HFD-540. /S/ 10/14/98
SUBJECT: Inquiry on Commercial Device

During the filing meeting for NDA 20-965, sponsor was contacted to clarify statements regarding the commercial device for this NDA. Sponsor stated that the commercial device manufacturing site, is ready for inspection.

The official statement of above was faxed into the division and also formally submitted. This allowed the NDA to be filed.

Conversation ended amicably.

cc:

NDA 20-965
HFD-540/Div File
HFD-540/Cintron
HFZ-410/Felten

**APPEARS THIS WAY
ON ORIGINAL**

TSI

TSI 5-16

Meeting Minutes

Date: November 4, 1996 Time: 1PM Location: N-225

IND: [redacted] Levulan(5-aminolevulinic acid HCL)Topical Solution

Type of meeting: End of Phase 2

Meeting Chair: Linda Katz, M.D., Deputy Director, HFD-540

Meeting Recorder: M.J.Kozma-Fornaro, Supv. Proj. Mgr., HFD-540
Olga Cintron, Project Manager, HFD-540

FDA Attendees:

- R.Srinivasan, Ph.D., Team Leader, Biostatistics, HFD-725
- Cheryl Dixon, Ph.D., Biostatistics, HFD-540
- Robin Anderson, R.N., MBA, Project Manager, HFD-540
- Abby Jacobs, Ph.D., Team Leader, Pharmacology, HFD-540
- Amy Nostrandt, Ph.D., Pharmacologist, HFD-540
- Ramzy Labib, M.D., Medical Officer, HFD-540
- Wilson DeCamp, Ph.D., Team Leader, Chemistry, HFD-540
- Janet Higgins, Chemist, HFD-540
- Bonnie B. Dunn, Deputy Director, HFD-830
- Linda Katz, M.D., Deputy Director, HFD-540
- M.J.Kozma-Fornaro, R.N., M.S.A., Supv. Project Manager, HFD-540
- Olga Cintron, R. Ph., Project Manager, HFD-540

Sponsor Attendees:

- Samuel Swetland, Consultant, Regulatory Affairs, Guidelines, Inc.
- Stuart L. Marcus, M.D., Ph.D., DUSA Pharmaceuticals, Inc.
- Russell S. Sobel, M.S., DUSA Pharmaceuticals, Inc.

[redacted]

- Allyn Golub, Ph.D., Technical/Regulatory Affairs, Guidelines, Inc.
- Geoffrey Shulman, M.D., President/CEO, DUSA Pharmaceuticals, Inc.

Meeting Objectives:

1. To discuss the completeness of the pharmacology, toxicology and chemistry, manufacturing and controls information.
2. To evaluate the adequacy of the Phase 2 studies and the adequacy of the proposed Phase 3 protocols to establish safety and effectiveness for the claimed indication.

Discussion points:

CHEMISTRY, MANUFACTURING AND CONTROLS:

The following comments were provided to the sponsor with respect to CMC:

1. Proposed specifications:

(A) Drug Substance

Additional parameters that should be considered are: pH, specifications of [redacted] identified on page 265-6 (namely [redacted] and [redacted] and a test for residual solvent should be provided, if applicable.

The UV spectra for the drug substance and key related substances that are potential [redacted] should also be provided.

Since there is no NDA for this drug substance, a full characterization of the drug substance should be provided. The sponsor may refer to February 1987 guidelines for submitting documentation in drug applications for the manufacture of the drug substance or may reference to a DMF which contains this information.

Please note that the drug substance manufacturer has no inspection history according to the sources consulted.

(B) Drug product and intermediates

The specifications provided on page 274-5 seem to be adequate at this time. However, examination of the full tests methods and the NDA as a whole will need to be performed before a full evaluation can be rendered.

2. Stability protocol:

(A) Drug substance

One set of regulatory specifications should be provided. The statement regarding to related substances specifications, also applies to this section.

Stability at 25 C/60% RH: An initial time point should

be provided. The two weeks and one month time period could be eliminated.

Stability at [] An initial time point should be provided and a two month time period should be added. The two week station could be eliminated.

Also, the drug substance should be stressed under a [] stress protocol.

(B) Drug product

The stability specifications were not described on page 281-7. The sponsor should clarify if they will be the same as the release specifications.

The sponsor should clarify if the product is tested in both states, the vehicle and drug substance and the reconstituted drug product.

The stability of activated applicators should be provided in the NDA.

3. Additional comments:

Labeling- The first paragraph of the DESCRIPTION section does not belong in this section. Also, this product, should not be labeled as a topical solution.

Please note the changes of light delivery system on page 239-40 of the package.

Letters of authorization should be provided for all DMF's referenced in the NDA.

PHARMACOLOGY/TOXICOLOGY

The following comments were provided to the sponsor by the pharmacologist:

The sponsor should perform a full genotoxicity test battery, including an in vitro cytogenetic test in mammalian cells, or cite studies addressing this from the literature. An in vivo test for test for chromosomal damage in rodent hematopoietic cells should be performed if significant systemic exposure is demonstrated after topical administration.

Photogenotoxicity testing should be performed.

Transdermal absorption should be performed, as part of the clinical trials to estimate systemic exposure. If this is minimal, then further toxicity testing may not be necessary. If there is significant systemic exposure, then the sponsor should perform testing in animals for: teratogenicity and ocular effects (e.g. tissue concentrations and photosensitivity). Alternatively, the sponsor may provide relevant clinical data.

- * The sponsor stated that genotoxicity and photogenotoxicity testing will be performed. Also, that some human (systemic) pharmacokinetic and in vitro transdermal absorption data was available as well as clinical data from patients with porphyrias that will be submitted. The pharmacologist clarified that if these data demonstrate lack of significant systemic absorption and/or adequately address the toxicity issues, they will be acceptable.

CLINICAL:

The following comments were provided by the medical officer:

The protocol included on page 152 and page 158 of the package is not clear whether the same patient may be treated on the scalp and on the face. This should be clarified. The sponsor agreed to clarify that the patient will be treated in only one site.

Blinding- In this situation, blinding is very difficult to achieve. Good photos properly identified should be taken to show the morphology and also as a backup for the investigator's evaluation. Photos should be taken for each patient that has been retreated in a specific site. Also, each center should have a list of investigators that will be blinded and unblinded before starting the study.

Primary Efficacy Criteria- The percent for improvement should be 75% to 80%.

Secondary Efficacy Criteria- Pigmentary characteristics such as hyper or hypopigmentation are not considered a secondary efficacy criteria. It is considered an adverse event. The secondary efficacy criteria should be adequately defined.

Laboratory evaluations- It is recommended that until the absorption of the drug has been assessed laboratory evaluations should be performed at 4 weeks instead of 8 weeks. Also, the

extent of use of the goggles should be defined in the protocol. Unless the systemic absorption and pharmacokinetic data shows otherwise, then the patient should wear goggles from drug dosing through treatment period and after treatment.

Exclusion criteria- On exclusion of thickened (hyperkeratotic) lesions, it should be identified in the first visit and recorded in the template. Also, it should be clarified whether they will be target lesions or not.

BIOSTATISTICS:

The following comments were provided by the biostatistician:

The protocol states that from 4-15 clinically typical target lesions of either the face or the scalp will be selected. The Agency inquired that if a patient has up to 15 lesions that are treatable, will all treatable lesions be treated or will a "target sample" of the total be treated. The sponsor clarified that all the target lesions (minimum of 4, maximum of 15) within the treatment field (face or scalp) will be treated and evaluated for response.

To prevent bias, two populations: ITT-LOCF (Intent-to-Treat, Last Observation Carried Forward) and per protocol should be analyzed. The ITT population should include every subject who was dispensed a study treatment (active or vehicle). Detailed definitions of the ITT-LOCF and Per Protocol Populations should be provided.

Pigmentary characteristics is considered an adverse event rather than an efficacy variable.

In the protocol under "Number of Patients", the randomization scheme needs to be clarified.

DEVICES:

The following comments were provided by the Supervisory Project Manager on behalf of the Center for Devices and Radiological Health:

From a device safety standpoint, it is recommended that the Phase 3 trial be initiated. However, the need for protective eyewear during treatment should be added to the baseline (Visit B) (UB only). Also, skin and eye photosensitivity should be addressed by the sponsor.

BIOPHARMACEUTICS:

Due to previous commitments, Dr. Dennis Bashaw was not able to assist to this meeting. The Agency will submit his comments to the sponsor as soon they become available.

The meeting ended cordially.

POST-MEETING CORRIGENDA:

Chemistry:

The degradation/synthetic pathways for potential [redacted] should be identified.

Alcohol content should be described as (v/v)% in the label and throughout the application.

Clinical:

The medical officer inquired if the drug was irritant to normal skin. The sponsor stated that it was not irritant to normal skin. The Agency feels that topical safety studies will be needed to show safety to neighboring normal skin.

Signature, minutes preparer: [redacted] /S/

Concurrence Chair: [redacted] /S/

**APPEARS THIS WAY
ON ORIGINAL**



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 2, 1999.

Number of Pages (including cover sheet) 2

TO: Mr. Sam Swetland, Vice President, Regulatory Affairs and Compliance

COMPANY: Guidelines, Inc.

NUMBER: 954-432-9015

MESSAGE: RE: NDA 20-965 Levulan Kerastick for Topical Solution, 20%

Please find a request for restatement of Phase 4 commitments.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.

TITLE: Project Manager

TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

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CC: NDA 20-965
HFD 540/DIV FILES

1 Page(s) Redacted

DRAFT

/S/

MEMORANDUM OF TELEPHONE CONVERSATION

JUL 27 1999

DATE: July 27, 1999
DRUG: Levulan
NDA: 20965
SPONSOR: Guidelines
Sam Swetland
FDA: Mary Jean Kozma-Fornaro **/S/** 7/27/99
CPMS, HFD 540
Subject: Fax dated 7/7/99 Questions for CMC reviewers

Mr. Swetland was contacted to provide an update to above fax. Regarding question 1 on the DMF amendment for EP specifications, further discussion at the Office level is necessary. This is also a review issue which needs Office input.

Regarding question 2, the clock starts with a complete response to the Approvable letter issues. Inspections will be requested at that time and the microbial testing facility would require an inspection. It is understood that there is a direct relation to the DMF question and complete response submission which impacts on when and how the sponsor submits the complete response.

Conversation ended amicably.

Copy of fax dated 7/7/99 attached.
cc:
NDA 20965
HFD 540-Div File
HFD 540-Cintron
HFD 830-Hathaway

**APPEARS THIS WAY
ON ORIGINAL**

GUIDELINES, INC.

FACSIMILE TRANSMITTAL SHEET

TO: OLGA CINTRON	FROM: Sam Swetland
COMPANY: DDDDP/ODEV/FDA	DATE: July 7, 1999
FAX NUMBER: 301-827-2075	TOTAL NO. OF PAGES INCLUDING COVER: 21
PHONE NUMBER: 301-827-2023	RE: Questions For The CMC Reviewers

URGENT FOR REVIEW PLEASE COMMENT PLEASE REPLY PLEASE RECYCLE

NOTES/COMMENTS:

As per our phone conversation, we are in the process of responding to the recent Approvable Letter for DUSA's NDA 20-965. To expedite this process, we would appreciate the opportunity to discuss the following issues with the CMC reviewers for NDA 20-965.

1. In the drug substance manufacturing process (synthesis and purification), will it be acceptable to utilize purified water that meets the EP specifications for Purified Water (revised 7/1/99) instead of "Purified Water USP". If acceptable, [redacted] will amend their Type II DMF to include the EP specification and test data for "Purified Water EP".
2. Will it be possible to respond to the Approvable Letter, reopening the review clock, pending the scheduling and re-inspection of the drug substance manufacturer? Additionally, will the Agency request an inspection of the microbial testing facility during this time.

As the answer to these questions will affect our ability to respond to the deficiencies in the Approvable Letter, we would appreciate the opportunity to discuss these issues with the Agency as soon as possible. Thanks for your assistance in this matter.



Sam Swetland

10320 USA Today Way,
Miramar, Florida 33025
(954) 433-7480, Fax (954)432-9015

Redacted 1

pages of trade

secret and/or

confidential

commercial

information



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 9, 1999.

Number of Pages (including cover sheet) 1

TO: Mr. Samuel D. Swetland

COMPANY: Guidelines Incorporated

NUMBER: 954-432-9015

MESSAGE:

RE: NDA 20-965 Levulan

The following information is requested from the medical officer:

1. Please clarify whether any target lesions in clinical studies ALA-018 or ALA-019 were located on patients' ears.

2. If any target lesions were located on patients' ears,

(a) were patients whose target lesions were located on their ears among the patients with face lesions, or among the patients with scalp lesions?

(b) How many target lesions were located on patients' ears?

(c) What was the lesion clearance rate for target lesions located on patients' ears?

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.

TITLE: Project Manager

TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

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cc: NDA 20-965
DIV FILES

MEMORANDUM OF TELEPHONE CONVERSATION

Date: March 3, 1999.

NDA: 20-965

Drug: Levulan Kerastick for Topical Solution, 20%

Sponsor: DUSA Pharmaceuticals

FDA participants: Richard Felten, Chemist, HFZ-410, CDRH 6/10/99.
Olga Cintron, Project Manager, HFD-540, CDER

External participant: Samuel D. Swetland, Vice President, Regulatory Affairs and Compliance, Guidelines Incorporated (authorized representative)

Subject: Drug/Device Split

The Agency contacted Guidelines, Inc., to inform them of the plans to separate the device portion from the drug/device package submitted in the NDA. The Agency indicated that the basis for implementing this administrative change was that, in the event that the application is approved as a combination drug/device package, it becomes very difficult for CDER to deal with device related issues. CDER does not have a defined tracking system to review device related adverse events, neither has the expertise to review modifications to a device.

The Agency indicated that the process was to be performed with the device related material that has been already submitted to the NDA. The documents would be transferred into a PMA application with a correspondent PMA number. CDRH will issue an acknowledgement letter for this purpose.

Guidelines, Inc. was advised that an approvable letter would be issued, since the PMA application is initiated with the date of the original submission, which is July 1, 1998. Subsequently, the final action would be issued simultaneously with the final action for the NDA. Regarding the Sponsor's planned commercial device amendment, CDRH indicated that this amendment will be reviewed if it is received on time for review prior to CDER's approval of the NDA. In the event that the commercial device amendment review cannot be completed before approval of the NDA, the amendment will be withdrawn and resubmitted as a PMA supplement to the approved PMA.

The Agency requested that if the Sponsor had any comments or concerns regarding this change, to let the Agency know by no later than March 10, 1999. Guidelines, Inc. agreed to contact the Sponsor and relay to the Agency any concerns regarding this issue.

The conversation ended cordially.

Signature, minutes preparer:

/S/

3/3/99.



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 1, 1999.
TO: Mr. Samuel D. Swetland
COMPANY: Guidelines, Inc.
NUMBER: 954-432-9015

Number of Pages (including cover sheet) 1

MESSAGE:

RE: NDA 20-965 Levulan

Please find medical officer's request for information:

1. With respect to Clinical Study ALA-018, please provide all the clinical slides of the following patients: 18102, 18103, 18106, 18116, 18117, 18216, 18221, 18301, 18302, 18501, 18510, and 18608.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

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cc: NDA 20-965
Div Files
AED-570/OKun
HFD-540/Cintron



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 11, 1999.
TO: Mr. Samuel D. Swetland
COMPANY: Guidelines
NUMBER: 954-432-9015

Number of Pages (including cover sheet) 3

MESSAGE:

RE: NDA 20-965 Levulan Kerastick for Topical Solution, 20%

Please find medical officer's response to questions (facsimile from Guidelines dated 1/8/99).

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

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cc. NDA 20-965
HFD-540/Olga
HFD-540/Cintron

**APPEARS THIS WAY
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NDA 20-965

Response to Sponsor's questions:

(1) Baseline in these footnotes refers to Baseline A (prior to drug application). Reviewer feels that with respect to the incidence of adverse effects, the time period of interest to clinicians and patients begins when drug is applied to lesions. If Baseline B were used, the table would not capture any adverse events that occurred between drug application and light exposure--and this time period is of clinical relevance.

(2) The reviewer has tabulated the maximum severity experienced by the patients at any time point between baseline A and 24 hours. The reviewer agrees that another title for this table is more appropriate. "Maximum Severity of Burning/Stinging Reported by Patients During PDT--ALA-018" may more accurately capture the meaning of the data presented in this table.

**APPEARS THIS WAY
ON ORIGINAL**

GUIDELINES, INC.

FACSIMILE TRANSMITTAL SHEET

TO: OLGA CINTRON	FROM: Sam Swetland
COMPANY: DDDDP/ODEV/FDA	DATE: January 8, 1999
FAX NUMBER: 301-827-2075	TOTAL NO. OF PAGES INCLUDING COVER: 1
PHONE NUMBER: 301-827-2023	RE: Clarification of Reviewer's Request

URGENT
 FOR REVIEW
 PLEASE COMMENT
 PLEASE REPLY
 PLEASE RECYCLE

NOTES/COMMENTS:

As per our phone conversation, DUSA will provide the analyses requested by the Medical Reviewer. To expedite this process, we would appreciate clarification of the following points.

1. Does "baseline" in the footnotes of these tables refer to Baseline A (prior to drug application) or Baseline B (prior to light treatment)? This distinction is most important for the table entitled "Post-PDT Cutaneous Adverse Events – ALA-018**."
2. For the table entitled, "Severity of Burning/Stinging During PDT – ALA-018**," has the reviewer tabulated the *maximum* severity experienced by the patients at any time point between baseline and 24 hours (including Baseline A through 24 hours after light treatment)? If this is the case, a more suitable title for the table may be, "Maximum Severity of Burning/Stinging Associated With PDT – ALA-018**."

Thanks for your assistance in this matter.

Sam Swetland

10320 USA Today Way,
Miramar, Florida 33025

(051) 422-7490 Fax (051) 422-0015



Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 5, 1999.
TO: Mr. Samuel D. Swetland
COMPANY: Guidelines
NUMBER: 954-432-9015

Number of Pages (including cover sheet) 5

MESSAGE:

RE: NDA 20-965 **Levulan Kerastick for Topical Solution, 20%**

Please find medical officer's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020

FAX NUMBER: 301-827-2075

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CC: NDA 20-965
HFD-540 / OK

**APPEARS THIS WAY
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1. Reviewer has tabulated and analyzed cutaneous adverse events (including unwanted PDT responses that occur and are detected) in the following manner, using data from the ALA-018 clinical study. Sponsor is requested to confirm reviewer's analysis of cutaneous adverse events for ALA-018, and to perform an analogous analysis of cutaneous adverse events for the other pivotal clinical trial (ALA-019):

ADVERSE EFFECTS DURING PDT—ALA-018*

Fraction of patients with some or all target lesions involved:	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
	SOME	ALL	SOME	ALL	SOME	ALL	SOME	ALL
Erythema†	12/72 (17%)	60/72 (83%)	11/21 (52%)	7/21 (33%)	3/16 (19%)	13/16 (81%)	4/8 (50%)	4/8 (50%)
Edema†	21/72 (29%)	5/72 (7%)	0/21	0/21	3/16 (19%)	3/16 (19%)	2/8 (25%)	0/8
Burning/Stinging	9/72 (13%)	32/72 (44%)	8/21 (38%)	2/21 (10%)	2/16 (13%)	14/16 (88%)	1/8 (13%)	2/8 (25%)

*defined as the prevalence of adverse events during the time period between baseline and 24 hours after light treatment

†Sponsor has not collected data that would permit the classification of these adverse events as mild, moderate, or severe.

SEVERITY OF BURNING/STINGING DURING PDT—ALA-018**

Degree of Severity:	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE
Burning/Stinging	30/72 (42%)	41/72 (57%)	10/21 (48%)	0/21	8/16 (50%)	8/16 (50%)	3/8 (38%)	0/8

**the fraction of patients who experienced burning/stinging on at least one target lesion up to (and not exceeding) the degree of severity indicated, during the time period between baseline and 24 hours after light treatment

POST-PDT CUTANEOUS ADVERSE EVENTS—ALA-018**

Degree of Severity:	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE	MILD/MODERATE	SEVERE
Scaling/Crusting	49/72 (68%)	1 (1%)	8 (38%)	0	9 (56%)	1 (6%)	3 (38%)	0
Pain	0	1 (1%)	0	0	0	0	0	0
Tenderness	2/72				1 (6%)			

	(3%)							
Itching	28/72 (39%)	2 (3%)	4 (19%)	0	5 (31%)	3 (19%)	2 (25%)	0
Edema	1/72 (1%)	0	0	0	0	0	0	0
Ulceration	4/72 (6%)	0	0	0	0	0	0	0
Bleeding/ Hemorrhage	2/72 (3%)	0	0	0	1 (6%)	0	0	0
Hypo/ hyperpigmentation ‡	18/72 (25%)	4/21 (19%)		5/16 (31%)		2/8 (25%)		
Vesiculation	3/72 (4%)	0	0	0	1 (6%)	0	0	0
Pustules	3/72 (4%)	0	0	0	0	0	0	0
Oozing	1/72 (1%)	0	0	0	0	0	0	0
Dysesthesia	2/72 (3%)	0	0	0	0	0	0	0
Scabbing	3/72 (4%)	1 (1%)	0	0	0	0	0	0
Erosion	7/72 (11%)	1 (1%)	0	0	0	0	0	0
Excoriation	1/72 (1%)							
Wheal/Flare	2/72 (3%)							
Skin disorder, NOS	5/72 (7%)	1 (1%)	1 (5%)	1 (5%)	1 (6%)	0	1 (13%)	0

**defined as adverse events that are not present at baseline and have not returned to baseline by 24 hours after light treatment

‡This category refers to the fraction of patients who develop hypo- and/or hyper- pigmentation on at least one target lesion during the treatment course. Sponsor has not collected data that would permit the classification of the hypo- and/or hyper- pigmentation as mild, moderate, or severe.

On page 051 of IND [redacted] sponsor has classified PDT responses for protocols ALA-018 and ALA-019 (see Attachment 1). Reviewer has clustered related PDT responses (e.g. hemorrhage and mild bleeding) in the same category (bleeding/hemorrhage) to eliminate clinically unimportant distinctions. The following PDT response events have been grouped together: crusting, scaling, and hyperkeratosis grouped into scaling/crusting; hemorrhage and mild bleeding grouped into bleeding/hemorrhage; pain and tenderness grouped into pain). Miscellaneous cutaneous adverse events (e.g. swollen cheek, warm sensation, herpes simplex, rash), which include together the adverse events by body system pertaining to the skin, along with PDT

responses, are classified as Skin disorder, NOS. If a patient had an event recorded at more than one visit, that patient is counted only once.

2. Sponsor is requested to provide the names of the unblinded investigators who participated in the clinical studies ALA-018 and ALA-019:

**APPEARS THIS WAY
ON ORIGINAL**

Attachment 1

PROTOCOL ALA-018

Number of Patients with PDT Response

Event	Levulan N= 88	Vehicle N=29
Erythema	87	24
Edema	32	1
Stinging/Burning	84	9
Crusting	35	2
Erosion	6	0
Excoriation	1	0
Hemorrhage	2	0
Hyperkeratosis	3	0
Hyperpigmentation	1	0
Itching	36	4
Mild Bleeding	1	0
Oozing	1	0
Pain	1	0
Pustules	3	0
Scabs	4	0
Scaling	35	7
Swollen Cheek	1	0
Tenderness	2	0
Ulceration	4	0
Vesiculation	3	0
Warm Sensation	1	0
Wheal/Flare	2	0

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL ALA-019

Number of Patients with PDT Response

Event	Levulan N= 93	Vehicle N=33
Erythema	93	26
Edema	38	0
Stinging/Burning	93	4
Bleeding	1	0
Blister	3	0
Burning	1	0
Crusting	53	0
Erosion	14	0
Hemorrhage	2	0
Itching	18	1
Pain	2	0
Pustules	2	0
Scabbing	1	0
Scaling	21	1
Ulceration	3	0
Vesiculation	5	0
Warm Sensation	1	0
Wheal/Flare	11	0

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: August 20, 1998

NDA: 20-965

DRUG: Levulan (aminolevulinic HCl) Kerastick for Topical Solution, 20%

SPONSOR: Guidelines Incorporated

Sam Swetland

Dr. Alan Gollup

FDA: Dr. Jonathan Wilkin, DD, HFD-540

Mr. Richard Felten, Reviewer, CDRH

Mary Jean Kozma-Fornaro, C, PMS, HFD-540

SI 10/14/98

SUBJECT: Inquiry on Commercial Device and Quality Control

Sponsor was contacted to provide further clarification of the commercial device manufacturing site and the connection with [redacted] is part of DUSA Pharmaceuticals and the Quality Control site for the commercial device. Sponsor confirmed that [redacted] is ready for inspection. Sponsor also confirmed that the Design Control Requirements, effective July, 1998, are incorporated in the commercial device. The sponsor has been in the process of implementing the DCR over the past year.

The commercial device data will be submitted approximately February, 1999. The sponsor was encouraged to submit sooner to facilitate the review process.

A fax communication and hard copy of the [redacted] address and statement of being ready for inspection was submitted on August 20, 1998

Conversation ended amicably.

cc:

NDA 20-965
HFD-540/Div File
HFD-540/Cintron
HFZ-410/Felten

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONFERENCE

DATE: August 18, 1998
NDA: 20-965
DRUG: Levulan (aminolevulinic HCl) Kerastick for Topical Solution, 20%
SPONSOR: Guidelines Incorporated
Sam Swetland
Dr. Alan Gollup
FDA: Dr. Jonathan Wilkin, DD, HFD-540
Mr. Richard Felten, Reviewer, CDRH
Mary Jean Kozma-Fornaro, C, PMS, HFD-540 **/S/** 10/14/98
SUBJECT: Inquiry on Commercial Device

During the filing meeting for NDA 20-965, sponsor was contacted to clarify statements regarding the commercial device for this NDA. Sponsor stated that the commercial device manufacturing site, _____ is ready for inspection.

The official statement of above was faxed into the division and also formally submitted. This allowed the NDA to be filed.

Conversation ended amicably.

cc:

NDA 20-965
HFD-540/Div File
HFD-540/Cintron
HFZ-410/Felten

**APPEARS THIS WAY
ON ORIGINAL**



**GUIDELINES
INCORPORATED**

FAXED
8-18-98

August 18, 1998

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852

**REFERENCE: New Drug Application for Levulan® (aminolevulinic acid HCl)
Kerastick™ for Topical Solution, 20% - NDA No. 20-965**

Dear Dr. Wilkin:

On behalf of our client, DUSA Pharmaceuticals, Inc., we herewith amend the subject application in accordance with 21CFR §314.60 to provide information requested by the Division during a telephone conversation with Sam Swetland on 18 August 1998. The following information is provided.

The Cover Page (page 10-002) of the Device Manufacturing Documentation submitted in the above referenced NDA stated that the device manufacturing facility, [redacted] would be available for FDA inspection in February of 1999. This statement referred to the anticipated date when the commercial design, the 4170 Blue Light Photodynamic Therapy Illuminator, would be complete and the manufacturing procedures for this design would be in place at the commercial device manufacturer's facility.

As pointed out by [redacted] during our phone conversation, an inspection of the documentation for the manufacture of the clinical devices will be necessary as part of the NDA review. We confirm that the documentation to support the

design and manufacture of the clinical devices is available at [redacted] and is ready for FDA inspection.

We trust that this clarification is satisfactory and that the application will be found acceptable for filing.

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

Sincerely yours,



Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
D:\SAMDA Documents\Cover Letter-3.doc

APPEARS THIS WAY
ON ORIGINAL

ELECTRONIC MAIL MESSAGE

Sensitivity: COMPANY CONFIDENTIAL

Date: 02-Dec-1999 10:33am EST
From: Olga Cintron
CINTRONO
Dept: HFD-540 CRP2 N248
Tel No: 301-827-2023 FAX 301-827-2075

TO: Steve Hathaway (HATHAWAYS)
TO: Wilson DeCamp (DECAMP)
CC: Jonathan Wilkin (WILKINJ)
CC: Mary Jean Kozma-Fornaro (KOZMAFORNARO)

Subject: NDA 20-965 Levulan

Tony:

Guidelines just called to provide a response to your question regarding the dimensions of the pictures that are included in the Levulan labeling.

DUSA indicated that they do not have a layout at this time, but that the pictures to be included in the final printed labeling would be no smaller than 1" X 1" square.

Olga

APPEARS THIS WAY
ON ORIGINAL

Printed by Olga Cintron
Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 05-Nov-1999 11:03am
From: Assadollah Noory
NOORYA
Dept: HFD-880 CRP2 N366
Tel No: 301-827-2507 FAX 301-827-2579

TO: Olga Cintron

(CINTRONO)

CC: Dennis Bashaw

(BASHAW)

CC: Assadollah Noory

(NOORYA)

Subject: NDA 20-965, Levulan kerastic, Revised Labeling Submission dated 10/1/1999

In the revised pharmacokinetics labeling submitted on October, 1 1999, the applicant has incorporated the recommendation made by DPE III in the Addendum review dated November, 19 1998. No further action is necessary by DPE III regarding NDA 20-965.

Assad Noory
DPE III

**APPEARS THIS WAY
ON ORIGINAL**

*cc: NDA 20-965
HFD-540/Div files*



GUIDELINES
INCORPORATED

ORIGINAL

11 March 1999

ORIG AMENDMENT

SU



Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
2nd Floor North (HFD-540)
9201 Corporate Boulevard
Rockville, MD 20850

**REFERENCE: NDA AMENDMENT - New Drug Application for Levulan®
(aminolevulinic acid HCl) Kerastick™ for Topical Solution, 20% -
NDA No. 20-965**

Dear Dr. Wilkin:

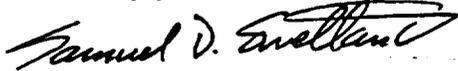
On behalf of our client, DUSA Pharmaceuticals, Inc., we herewith amend the subject application in accordance with 21CFR §314.60 to provide an NDA Safety Update for the subject application. The only clinical study performed under IND [redacted] since the NDA was submitted is Protocol ALA-012, "A Phase I/II study of Photodynamic Therapy with Levulan (5-Aminolevulinic Acid HCl) Topical Solution and Visible Red Light for the Removal of Hair". The Integrated Summary of Safety provided in the original NDA included data on 11 patients from this study. This update includes safety information on the initial 11 patients previously reported and the remaining 19 patients who were treated subsequent to the NDA analyses.

It is DUSA's opinion that this update does not change the statements and conclusions made in the NDA Integrated Summary of Safety since Protocol ALA-012 involved a different indication, different treatment conditions and different light sources than the pivotal trials.

If you need any further information regarding this document, please feel free to contact me at (954) 433-7480.

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or USC, Section 331j.

Sincerely yours,



Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

Enclosure:
NDA Safety Update

SDS/sds
DUSA \ Final NDA Documents \ Cover Letter -15.doc

**APPEARS THIS WAY
ON ORIGINAL**

144 Page(s) Redacted

DRAFT

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 19, 1999 [redacted] /S/

FROM: Karen Lechter, HFD-42 ✓

TO: Olga Cintron, HFD-540

SUBJECT: Levulan Kerastick for Topical Solution + blue light PDT
NDA 20-965

I have a number of comments on the proposed PPI for this product. I have highlighted my thoughts in this memorandum and have attached a rewritten PPI that is consistent with my comments. In the attached proposed PPI, I have shaded areas about which I have questions.

I have reorganized the information under headings that are consistent with the headings we have been using for other recent PPI's. These headings are based on the organization that is mandated for Medication Guides. Although this is not a Medication Guide, we believe the flow of the information and the section headings for Medication Guides reflect how consumers are best able to process information and therefore these headings are also appropriate for PPI's. I have simplified the language where possible. I have changed headings from all upper case to upper and lower case, which is easier to read.

The sponsor has included a first section entitled [redacted]
[redacted] This section is required in Medication Guides, but it is not necessary in all PPI's. In fact, most of them do not have such a section. Such a section is intended to convey very important information for the patient to understand about the drug. I have not included the section in my proposed PPI that is attached because I believe this information is adequately conveyed in other sections of the PPI. However, if the sponsor or your division wants to retain this section, it should be shortened considerably so it is punchy and contains a brief statement about protection from light during and after treatment.

The information that was originally in the section [redacted] is not necessary. It provides information about efficacy. However, if it is included, it should be simplified. I have included it in the section "What is?" However, the statistical presentation may confuse some readers. I am not sure it is necessary. You may want to eliminate it. If it is presented, it should include not just a single percentage, but a range based on the totality of studies in the PI. In my proposed PPI, I have used

figures from Table 1 in the PI representing improvement on the scalp or face, not total improvement for both together. However, if statistics about efficacy are used, your division may want to use different statistics from the PI.

In the section about who should not use the product, I was not clear what the difference was between the second and third conditions (porphyrias and allergies to chemicals called porphyrins). These items should be examined for redundancy and if the term "porphyrias" is used, it should be explained.

The statement about the effects on the ability to have children is not clear. Does it refer to men and women? Only to pregnant women? Is it appropriate here? In the PI, it is not connected with pregnancy as it was in the sponsor's proposed PPI. You should consider whether this information is appropriate for a PPI. If it is, the statement needs clarification and should be separate from the pregnancy warning.

I left out the statement about its not having been tested on persons with blood-clotting effects because I believe this information is not useful to patients.

I did not know if other side effects should have been included, based on information in the side effects tables of the PI. These include itching, changes in skin color and breakdown (erosion) of the skin (is this the same as flaking, that is mentioned in the PPI?). These should be included if appropriate. I included them, but you may want to consider if they are appropriate and explain or reword skin breakdown (erosion) if it is kept.

The name of the product should be consistent throughout the document. In some places, it is called "Levulan Kerastick for Topical Solution + blue light PDT." In other places it is called "Levulan PDT" or "Levulan Topical Solution." It would be less confusing for readers if there is some consistency. I have not been consistent in my attached PPI because I was not sure of the best wording to use in each instance.

I would like to add another comment that relates to the PI, which I mentioned briefly at the meeting today. In the PPI, there is a section entitled "Information to Patients." It is written as if it were directed to patients themselves, and not to health care professionals. For example, it refers repeatedly to "you," meaning the patient. Normally, this section in the PI is directed to health care professionals. It is entitled "Information for Patients" and provides the health care professional with a summary of information that should be conveyed to patients by the professional. However, it is not written to the patients. In the case of the Levulan labeling, it is confusing to have both a PPI for the patients and a PI section "Information to Patients" because the latter may be misinterpreted. Health care providers may mistakenly give patients copies of the PI section for patients rather than the PPI. This would be a problem, because, as now written, this section of the PI is not written in language that is easily understandable by consumers. I recommend that the PI section be rewritten to be "Information for Patients" and that references to "you" and other language suggesting that patients are reading it be changed. The PPI should be given to patients rather than the "Information for Patients" section of the PI. If the

review division wants to maintain this section as one that is directed to patients, it must be rewritten to make it more understandable to non-professionals. Some of the language can be simplified.

Please let me know if you have any questions. If I am unavailable, Nancy Ostrove can help you.

**APPEARS THIS WAY
ON ORIGINAL**

cc:
HFD-42/Lechter/Ostrove/Tabak/Roberts/Reading
NDA 20-965

KLlechter 11/19/99

NON-RELEASABLE

**APPEARS THIS WAY
ON ORIGINAL**

3 Page(s) Redacted

Draft

Labeling

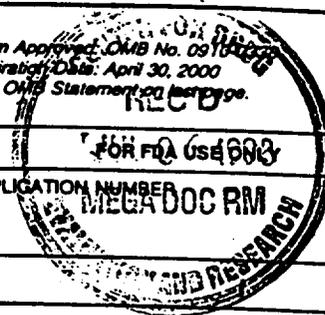
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0001
Expiration Date: April 30, 2000
See OMB Statement of Management

FOR FRA USE 1998

APPLICATION NUMBER
MEGA DOC RM



APPLICANT INFORMATION

NAME OF APPLICANT

DUSA Pharmaceuticals, Inc.

DATE OF SUBMISSION

June 29, 1998

TELEPHONE NO. (Include Area Code)
(914) 747-4300

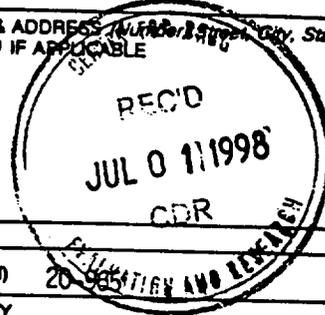
FACSIMILE (FAX) Number (Include Area Code)
(914) 747-7563

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

400 Columbus Avenue
Valhalla, NY 10595

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Guidelines, Inc.
10320 USA Today Way
Miramar, FL 33025



PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Aminolevulinic Acid HCl

PROPRIETARY NAME (trade name) IF ANY

Levulan^R KerastickTM

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

5-amino-4-oxopentanoic acid

CODE NAME (if any)

5-AIA HCl, 5-AIA, AIA

DOSAGE FORM:
Solution

STRENGTHS:

20%

ROUTE OF ADMINISTRATION:

Topical

PROPOSED INDICATION(S) FOR USE:

treatment of actinic keratoses of the face and scalp

INDICATION INFORMATION

APPLICATION TYPE
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug
Holder of Approved Application

TYPE OF SUBMISSION
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

New Drug Application for Approval

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 123

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment to Form FDA 356h

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment to Form FDA 356h

HHS NEWS

U.S. Department of Health and Human Services

P99-31
FOR IMMEDIATE RELEASE
December 6, 1999

FOOD AND DRUG ADMINISTRATION
Print Media: 30
Broadcast Media: 30
Consumer Inquiries: 88

FIRST DRUG DEVICE COMBINED TREATMENT FOR CERTAIN PRE-CANCEROUS SKIN LESIONS APPROVED

The Food and Drug Administration today announced the approval of **Levulan** <Kerastick> (aminolevulinic acid HCl) for Topical Solution, 20%, to be used in conjunction with photodynamic therapy for treatment of actinic keratoses (AKs)(pre-cancerous skin lesions) of the face or scalp. It is the first combined drug and device treatment designed for targeted treatment that can be limited just to the lesion site(s).

AKs are rough, scaly, red or brown patches that begin on the surface of the skin. They are mostly found among light-complected individuals -- affecting over 50% of elderly fair-skinned persons in hot, sunny climates. They can also be found more rarely in individuals in their teens and twenties.

Untreated, AKs may become malignant.

"Almost half of the estimated 5 million cases of skin cancer began as AKs. We hope that early detection and treatment of AKs may reduce the number of cases of skin cancer. This novel treatment offers a less invasive treatment alternative for AKs," said Dr. Jane Henney, Commissioner for Food and Drugs.

The <Levulan> <Kerastick> is a two-stage treatment process which involves the topical application of aminolevulinic acid by a doctor directly to the individual AK lesions, followed 14 to 18 hours later by photodynamic therapy. Photoactivation of treated AKs is accomplished with blue light irradiation utilizing a special light source designed to provide a uniform distribution of blue light to the affected face or scalp areas.

The <Levulan> <Kerastick> dosage form was designed to treat individual AKs lesions, thereby reducing possible skin irritation of unaffected, non-lesional skin. It is not currently indicated for the treatment of AKs of the back and arms.

In controlled clinical trials, the most common adverse event associated with treatment was local discomfort (stinging/burning sensation) during light treatment.

Other treatments for AKs include cryosurgery (freezing the skin), curettage (scraping), electrosurgery, excision, dermabrasion, laser surgery, and topical chemotherapy.

Medical experts still recommend that the best method of combating skin cancer is prevention. Common sense measures such as wearing protective clothing, avoiding the midday sun, and wearing sunscreen with a Sun Protection Factor (SPF) of at least 15 is still the best defense against skin cancer.

Aminolevulinic acid HCl is marketed by DUSA Pharmaceuticals, Inc of Valhalla, NY and will be marketed under the trade name LEVULAN KERASTICK for Topical Solution, 20%. It is to be marketed in combination with the light source BLU-U Blue Light Photodynamic Therapy Illuminator.

####

FDA HOME PAGE

Printed by Olga Cintron
Electronic Mail Message

Subject: COMPANY CONFIDENTIAL

Date: 09-Apr-1999 01:52pm
From: Martin Okun
OKUNM
Dept: HFD-540 CRP2 N241
Tel No: 301-827-2021 FAX 301-827-2075

TO: Olga Cintron

(CINTRONO)

Subject: April 08 labeling changes

See attached.

Marty

**APPEARS THIS WAY
ON ORIGINAL**

2 Page(s) Redacted

Draft

Labeling

Printed by Olga Cintron
Electronic Mail Message

Security: COMPANY CONFIDENTIAL

Date: 20-May-1999 03:54pm
From: Martin Okun
OKUNM
Dept: HFD-540 CRP2 N241
Tel No: 301-827-2021 FAX 301-827-2075

TO: Olga Cintron

(CINTRONO)

Subject: Revised Levulan Label

Hi Olga,

Please see attached.

Marty

**APPEARS THIS WAY
ON ORIGINAL**

20 Page(s) Redacted

Draft

Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: June 25, 1999

JUN 25 1999

To: Chi-wan Chen
Division Director, DNDC III

From: J. Steve Hathaway, Ph.D.
Review Chemist, HFD-540

Through: Wilson H. Decamp, Ph.D.
Chemistry Team Leader, HFD-540

VS/6/25/99

Subject: Addendum to Chemistry review of NDA 20-965 for Levulan Kerastick

Based on further discussion, the following are revisions to my review:

(1) Regarding the regulatory specifications for Related Substances in the drug substance, the specification does not follow the conventions set forth in the ICH Q3A guidance document "Impurities in New Drug Substances". "Related Substances" should be categorized as "Specified", "Unspecified" and "Total Impurities".

(2) Regarding the regulatory specifications for Related Substances in the drug product, the specification does not follow the conventions set forth in the ICH Q3B guidance document "Impurities in New Drug Products". "Related Substances" should be categorized as "Specified", "Unspecified" and "Total Impurities".

The following are additional deficiencies for the AE letter:

[Redacted]

[Redacted]

[Redacted] /S/

6/25/99

Steve Hathaway

- cc: Orig. NDA 20-965
HFD-540/DivisionFile
HFD-540/Chem/JS Hathaway
HFD-540/Chem Team Ldr/WH DeCamp
HFD-540/Div Dir/J Wilkin
HFD-830/Div Dir/CW Chen
HFD-540/Med Offr/M Okun
HFD-540/Pharm Tox/L Reidd
HFD-540/Proj Mgr/O Cintron
HFD-805/Micro/PCooney
HFD-805/Micro/BRiley
HFD-/BioPharm/DBashaw

APPEARS THIS WAY
ON ORIGINAL

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE**

**Friday,
November 5, 1999**

**Ballroom
Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland**

**FRIEDMAN & ASSOCIATES, COURT REPORTERS
11923 Parklawn Drive, Suite 203
Rockville, MD 20852
(301) 881-8132**