CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

CORRESPONDENCE

Printed by Olga Cintron

Electronic Mail Message

S **vity:** COMPANY CONFIDENTIAL

Date: 06-Apr-1999 03:05pm
From: Patricia Tuegel
TUEGELP
Dept: HFD-805 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

TO: Olga Cintron (CINTRONO)

Subject: NDA 20-965

Your consult request for the above application has been assigned to Review Microbiologist Bryan Riley on 4/5/99. Please make sure the COMIS assignment for microbiology is updated with the correct reviewer.

Microbiology Staff, HFD-805

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
Peter Cooney HFD-160		Olga Cintron HFD-540	
DATE: 3/10/99	IND NO.	NDA NO. 20-965	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 29, 1998.
NAME OF DRUG Lemtrada Kenstick	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE —
NAME OF FIRM DUSA Pharmaceuticals			

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(Specify below)*

New NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ LUTION
- ☐ VAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please find Volume 1.1 (disk copy) and Volumes 1.3 thru 1.5 of this new NDA for your review & comments (P 3-292 293). The division is planning to issue an action by the end of May 1999.

Your help is greatly appreciated.

/S/

SIGNATURE OF REQUESTER /S/ 3/10/99

METHOD OF DELIVERY *(Check one)* ☑ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Printed by Olga Cintron

Electronic Mail Message

S. .vity: COMPANY CONFIDENTIAL

Date: 16-Sep-1998 04:20pm
From: Olga Cintron
CINTRONO
Dept: HFD-540 CRP2 N248
Tel No: 301-827-2023 FAX 301-827-2075

TO: Steve Hathaway (HATHAWAYS)

CC: Wilson DeCamp (DECAMP)
Subject: NDA 20-965 Levulan

Steve:

Please advise if a CMC micro consult is needed for this NDA. If that's the case, then we should send the consult as soon as possible.

Thanks, Olga

APPEARS THIS WAY
ON ORIGINAL

Printed by Olga Cintron

Electronic Mail Message

ity: COMPANY CONFIDENTIAL

Date: 23-Apr-1999 02:51pm
From: Martin Okun
OKUNM
Dept: HFD-540 CRP2 N241
Tel No: 301-827-2021 FAX 301-827-2075

O: Olga Cintron (CINTRONO)

ubject: Re: NDA 20-965 Levulan

o concerns

arty
Marty:

Dr. Carreras, from the DSI, informed me that no inspections will be issued for this NDA. Do you have any concerns?

Olga

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES, INC.

FACSIMILE TRANSMITTAL SHEET

TO O a Cintron	FROM: Sam Swetland
COMP NY: D DDP/ODEV/FDA	DATE: December 3, 1999
FAX N MBER: 30 -827-2075	TOTAL NO. OF PAGES INCLUDING COVER: 5
PHON NUMBER: 30 -827-2023	RE: NDA 20-965

☐ URG NT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES OMMENTS

Dear lga,

As per our phone conversation, attached is the cover letter of the NDA Amendment agreeing to the labeling changes.

Sam Swetland

APPEARS THIS WAY
ON ORIGINAL

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

BEST POSSIBLE COPY

GUIDELINES INCORPORATED

BEST POSSIBLE COPY

Sent Via Facsimile

December 3, 1999

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® KERASTICK™ (aminolevulinic acid HCl) 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 order to respond to the Agency's Facsimile Transmission from Olga Cintron dated December 3, 1999.

DUSA Pharmaceuticals, Inc., agrees to the labeling modifications proposed by the Agency for the LEVULAN KERASTICK for Topical Solution, 20% as communicated in the Facsimile Transmission dated December 3, 1999.

We trust that this commitment is adequate and the application may be approved. If you need any further information, 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.

0320 US Today Way, Miramar, FL 33025, USA • 954-433-7480 • Fax: 954-432-9015 • E-mail: gis@gate.net

Since ly yours,

Samu l D. Swetland
Vice P esident, Regulatory Affairs and Compliance

SDS/sds
Enclosur

DUSAV\na 1A Documents\Cover Letter29.doc

GUIDELINES, INC.

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
Olga Cintron	Sam Swetland
COMPANY:	**DATE:**
DDDDP/ODEV/FDA	December 2, 1999
FAX NUMBER:	**TOTAL NO. OF PAGES INCLUDING COVER:**
301-827-2075	7
PHONE NUMBER:	**RE:**
301-827-2023	NDA 20-965

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Dear Olga,

As per our phone conversation, attached is the cover letter of the NDA Amendment to restating the Phase 4 commitments. The original of this submission (in duplicate) was submitted today for delivery on Friday 12-3-99.

If you did not receive this shipment, please let me know. Thanks

Sam Swetland

APPEARS THIS WAY
ON ORIGINAL

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

GUIDELINES INCORPORATED

December 2, 1999

Sent Via Facsimile

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® KERASTICK™ (aminolevulinic acid HCl) 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 order to respond to the Agency's request for restatement of Phase 4 clinical commitments as communicated in the Facsimile Transmission from Olga Cintron dated December 2, 1999.

DUSA Pharmaceuticals, Inc., agrees to perform the following Phase 4 studies.

1. A study to characterize the potential for dermal allergenicity of LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%. This study will be completed within 24 months of approval.

2. A study to characterize the safety and efficacy of LEVULAN KERASTICK for Topical Solution, 20%, plus blue light photodynamic therapy in an additional 70 patients in which at least 30 patients should have Fitzpatrick skin type IV-VI. Patients will be seen in follow-up at one year after treatment to assess the long-term recurrence rate of actinic keratoses that have resolved after treatment. This study will be completed within 4 years of approval.

3. A clinical study involving long-term (at least 12 months) follow-up of treated patients to characterize the recurrence rate of AK lesions that cleared by the primary endpoint (e.g., 8 weeks) and to characterize the histopathology of AK

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lesions in long-term follow-up. In this regard, the study will be designed to reject the hypothesis that AK lesions that are (a) assessed as completely cleared by clinical evaluation; (b) assessed as completely cleared by clinical examination but recur during follow-up; and (c) assessed as not completely cleared by clinical examination carry an increased risk of either (1) atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures at 12 month follow-up, or (2) squamous cell carcinoma of the skin at 12 month follow-up. DUSA will estimate the spontaneous incidence of progression of actinic keratoses to full thickness epidermal atypia or squamous cell carcinoma of the skin based on a review of the relevant scientific literature, and based on this estimate, will characterize the histopathology of enough treated lesions to preclude the possibility that a clinically significant fraction of completely cleared, completely cleared but recurrent, or not completely cleared lesions undergo malignant progression to full thickness epidermal atypia or to squamous cell carcinoma of the skin during long-term follow-up. This study will be completed within 4 years of approval.

As noted in the December 2, 1999 Facsimile Transmission, the commitments in items 2 and 3 above may be accomplished in a single study. Furthermore, DUSA will confer with the Agency regarding the design and acceptability of the proposed Phase 4 studies.

We trust that this information adequately responds to the requested information. If you need any further information, 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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
Enclosure:

DUSA\Final NDA Documents\Cover Letter-28.doc

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PLICATION 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	DATE OF SUBMISSION
DUSA Pharmaceuticals, Inc.	December 02, 1999
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
Phone: (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)*	PROPRIETARY NAME *(trade name)* IF ANY
Aminolevulinic Acid HCl	Levulan® Kerastick™
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 actinic keratoses of the face and scalp

JCATION 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

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — **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 ...ation)

See Attachment to Form FDA 356h

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Samuel D. Swetland	Samuel D. Swetland Vice President, Regulatory Affairs	12-02-99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
10320 USA Today Way, Miramar, FL 33025	(954) 433-7480

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DO NOT RETURN this form to this address.

FORM FDA 356h (4/97)

ATTACHMENT TO FORM FDA 356h

ESTABLISHMENT INFORMATION:

Drug Substance

The drug substance will be manufactured, packaged, controlled and shipped by [redacted] the drug substance manufacturer. Stability studies of the drug substance will be conducted by [redacted]

Name and Address of Manufacturing Site: [redacted]

Establishment Registration No.: Not Applicable

Contact Person and Phone No.: [redacted]

Site Inspection by FDA: This facility has been inspected.

Drug Product

The drug product will be manufactured, packaged, labeled, controlled and shipped by North Safety Products will be responsible for the manufacture of the bulk solution vehicle, filling and sealing of the glass ampules and assembly of the Levulan Kerastick. North Safety Products is responsible for the in-process testing of the bulk Levulan Topical Solution Vehicle.

Name and Address of the Manufacturing Site:

North Safety Products
2000 Plainfield Pike
Cranston, RI 02921

Establishment Registration No.: #1217998

Contact person and Phone No.: Jonny Smith
Manager, Business Quality
(401) 946-4400

Site Inspection by FDA: This facility has been inspected.

Contract Laboratories

The raw materials, process intermediates and finished products are analyzed by a contract analytical laboratory. The finished product stability studies are also conducted by the contract laboratory listed below:

Guidelines Analytical Laboratories, Inc. (GAL)
10320 USA Today Way
Miramar, FL 33025
DMF No.:

Establishment Registration No.: #1052961

Contact Person and Phone No.: Mike Ray
President
(954) 433-7480

Site Inspection by FDA: This facility is ready for inspection.

The finished product is tested for microbial content by the contract microbiological testing laboratory listed below:

Establishment Registration No.:

Contact Person and Phone No.:

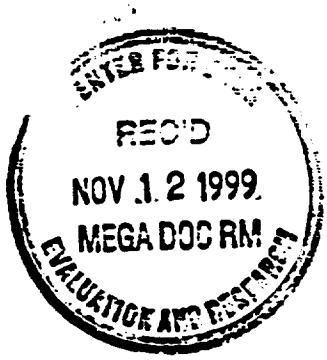
Site Inspection by FDA: This facility is ready for inspection.

CROSS REFERENCES:

DUSA's IND for Aminolevulinic Acid HCl: IND #
GAL's DMF: DMF #
DMF: DMF #
DMF: DMF #
DMF: DMF #

ORIGINAL

GUIDELINES INCORPORATED



November 11, 1999

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

ORIG AMENDMENT
/S/

REFERENCE: NDA AMENDMENT - New Drug Application for LEVULAN® KERASTICK™ (aminolevulinic acid HCl) 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. This amendment provides the draft Patient Package Insert (PPI) as agreed to following the recent Advisory Committee meeting. Four copies of the draft PPI and an electronic copy are provided for your review.

Additionally, in conversations with Richard Felten, he recommended that DUSA review both the Physician's Insert and the device Operating Instructions to assure that the sections referring to the device trade name and patient positioning during light treatment utilize consistent language. Therefore, attached is a red-lined version of the Physician's Insert (revision date October 1, 1999) modified to be consistent with the device labeling. This Physician's Insert does not include changes resulting from the DODAC meeting as it was our agreement that DDDDP would be making such revisions. Please incorporate the minor changes provided in the attached into the insert that DDDDP is drafting.

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

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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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
Enclosure:
Patient Package Insert
Diskette containing Electronic Labeling

DUSA\Final NDA Documents\Cover Letter-27.doc

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

October 11, 1999

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

/S/

REFERENCE: NDA AMENDMENT - New Drug Application for LEVULAN® KERASTICK™ (aminolevulinic acid HCl) 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. This amendment incorporates by reference a Drug Master File amendment submitted by the drug substance manufacturer,

On August 11, 1999 submitted an amendment to their Type II DMF for 5-aminolevulinic acid HCl, DMF No. This amendment contains responses to the comments forwarded to by the Office of New Drug Chemistry as a result of the CMC review of the above NDA application. The amendment also includes updated stability data and minor changes such as, use of Purified Water EP versus Purified Water USP, use of new identical manufacturing equipment, a new packaging container size and clarifications to the specifications for the processing ingredients. These changes are considered minor and do not affect the quality of the drug substance.

A summary of the new information is provided in the attached document provided by the DMF holder. For more details regarding this DMF amendment, please refer to DMF A letter authorizing the FDA to review DMF on behalf of

ORIGINAL

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this NDA was provided in the original NDA submission and a copy is attached to this submission for ease of review.

If you need any further information, 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

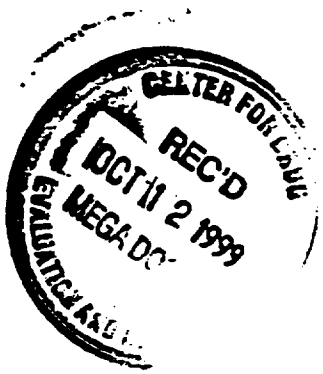
SDS/sds
Enclosure:
Summary of DMF Update

DUSA\Final NDA Documents\Cover Letter-26.doc

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

GUIDELINES INCORPORATED



NEW CORRESP

NC

October 8, 1999

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

Dear Dr. Wilkin:

On behalf of our client, DUSA Pharmaceuticals, Inc., enclosed please find the information requested during a telephone conversation on 7 October 1999 between Olga Cintron of your Division and Sam Swetland of Guidelines, Inc.

As requested, electronic copies of the revised draft labeling provided in the 1 October 1999 NDA Amendment is being provided to aid in the review of the application. This labeling includes the Package Insert, Carton Labels (cartons of 1, 4, 6 and 12 units) and individual Applicator Label (cardboard sleeve label). The requested files are provided as detailed below.

Diskette Title	File Name	File Description
LEVULAN® KERASTICK™ Draft Product Labeling October 1, 1999	Package Insert 10-1-99.doc	Draft Package Insert
	Kerastick Labels 10-99.doc	Draft LEVULAN® KERASTICK™ Carton labeling (cartons of 1, 4, 6, and 12 applicators) and Applicator label

Additionally, Ms Cintron requested 5 desk copies of the October 1, 1999 NDA Amendment. These desk copies are being provided as part of this submission.

10320 USA Today Way, Miramar, FL 33025, USA • 954-433-7480 • Fax: 954-432-9015 • E-mail: gis@gate.net

If you need any further information regarding these documents, please feel free to contact me.

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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

Enclosure:

1 Diskette – Levulan Kerastick Draft Product Labeling, October 1, 1999
5 Desk Copies – October 1, 1999 NDA Amendment

SDS/sds
DUSA\NDA Documents\Cover Letter-25.doc

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

AZ

October 1, 1999

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® KERASTICK™ (aminolevulinic acid HCl) 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 §314.110, responding to the June 27, 1999 action letter issued by the Office of Drug Evaluation V for LEVULAN® KERASTICK™ (aminolevulinic acid HCl) for Topical Solution, 20%. The attached amendment provides a complete response to each item listed in the June 27, 1999 action letter and contains the following information:

1. Information to support that all manufacturing and testing facilities have received satisfactory pre-approval inspections or have adequate inspectional histories to conclude that the facilities are in substantial conformance with current Good Manufacturing Practices regulations.

2. Revised draft labeling reflecting the recommendations provided by the Agency in the June 27, 1999 Approvable Letter.

3. A commitment to characterize the potential for dermal sensitization of LEVULAN KERASTICK for Topical Solution, 20%.

4. A commitment to characterize the safety and efficacy of LEVULAN KERASTICK for Topical Solution, 20% plus blue light photodynamic therapy in different skin types, including Fitzpatrick skin types IV-VI, and to

Location of page 004 of this submission.

Location of page 005 of Oct 1, 1999 Submission.

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Nov. 4

assess the long term recurrence rate of AK lesions over a 12-month follow-up period.

5. A justification for not undertaking characterization of the safety and efficacy of LEVULAN KERASTICK for Topical Solution, 20% plus blue light photodynamic therapy, delivered by the BLU-U™ blue light photodynamic therapy illuminator, for the treatment of actinic keratoses of the back and arms.

6. Revised drug substance and drug product specifications to conform to the ICH Q3A and Q3B guidance with respect to the nomenclature for [redacted] and a commitment to re-evaluate the specification limits for [redacted] once adequate data is available.

7. Updated safety information including data obtained from indications, dosage forms and dosage levels other than those currently being sought in the subject application.

8. Additional information to support the inclusion of an applicator cap as a tertiary component of the container-closure system to protect the applicator tip during the distribution, storage, and admixing of the LEVULAN KERASTICK in the physician's office.

We trust that this information adequately responds to all items listed in the action letter, and request that the review of this application be reopened. Based on the information provided, we believe that this resubmission meets the requirements of a Class 1 Resubmission under CDER's Manual of Policies and Procedures (MAPP 6020.4) and, therefore, request that it be assigned a 2-month performance goal. If you need any further information, 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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
Enclosure:

DUSA\Final NDA Documents\Cover Letter-24.doc

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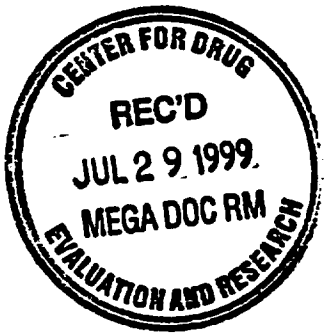
GUIDELINES INCORPORATED

28 July , 1999



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

NEW CORRESP

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

Dear Dr. Wilkin:

As requested by Mary Jean Kozma-Fornaro on July 27, 1999, and on behalf of our client, DUSA Pharmaceuticals, Inc. we herewith submit copies of the attached correspondence, previously forwarded to the Agency by telefax on July 7, 1999 and July 13, 1999.

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,

Allyn L. Golub, PhD
Chairman

ALG/br

Enclosures

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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

REC'D
JUL 29 1999

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DUSA Pharmaceuticals, Inc.	07/28/99
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(914) 747-4300	(914) 747-7563
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
400 Columbus Avenue Valhalla, NY 10595	Guidelines, Inc. 10320 USA Today Way Miramar, FL 33025 Phone: (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)*	PROPRIETARY NAME *(trade name)* IF ANY
Aminolevulinic Acid HCl	Levulan® Kerastick™
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	**CODE NAME** *(If any)*
5-amino-4-oxopentanoic acid	5-ALA HCl, 5-ALA, ALA

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	20%	Topical

(PROPOSED) INDICATION(S) FOR USE:

Treatment of actinic keratoses of the face and scalp

APPLICATION 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: Request for Agency Opinion

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — 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

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, 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: 2 /
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.

S. Swetland

Sam Swetland

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

GUIDELINES, INC.

FAXED 7/13/99

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
OLGA CINTRON	Sam Swetland
COMPANY:	DATE:
DDDDP/ODEV/FDA	July 13, 1999
FAX NUMBER:	TOTAL NO. OF PAGES INCLUDING COVER:
301-827-2075	8
PHONE NUMBER:	RE:
301-827-2023	Information for Chemist's Review

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Dear Olga,

As requested during our phone conversation yesterday, the following is additional information regarding the acceptability of Purified Water EP in the manufacture of the drug substance.

The USP specification for Purified Water has changed several times over the last 4 years (see Table 1). It has evolved from strictly off-line chemical tests to a mixture of off-line chemical tests and on-line tests, and finally to the current specification of all on-line testing (Total Organic Carbon and Conductivity).

The EP specification for Purified Water has also been recently revised (see attached translation of EP monograph – effective 7/1/1999 and French original). A comparison of the USP and EP Purified Water Specifications are provided on the attached table. The primary difference between the two pharmacopeial monographs is the conductivity specification. The USP specifies a Conductivity limit of 1.1 µS/cm at 20° C while the EP specifies a limit of 4.3 µS/cm at 20° C.

Other minor differences between the pharmacopeial monographs are the use of the Total Organic Carbon (TOC) test for the USP versus the Oxidizable Substances Test or TOC for the EP. The addition of limits testing for Heavy Metals and Nitrates are also in the EP.

The EP monograph specifies tests and limits for Microbial Contamination where the USP does not. However, the USP implies that Purified Water is protected from microbial contamination and appropriate microbial monitoring shall be done.

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The Purified Water EP proposed for use by the drug substance manufacturer, [redacted] is produced from the municipal [redacted] water supply. The conductivity of the incoming water is approximately 270 µS/cm mainly due to Ca, Mg, CO3 and SO4. The water is first softened over NaCl to replace the Ca, Mg, and etc. ions with Na and Cl ions. Finally, the water passes through a [redacted] Chloride ions are carried through the system thus causing the conductivity to be in the range of [redacted] µS/cm at 20° C.

The estimated chloride content of water meeting the USP conductivity specification of 1.1 µS/cm is approximately [redacted] ppm. The estimated chloride content of water meeting the EP monograph of 4.3 µS/cm is approximately [redacted] ppm.

In the ALA manufacturing process [redacted] of purified water is utilized. Using Purified Water EP, approximately [redacted] of chloride would be introduced. However, the process also utilizes [redacted] Kg of [redacted] Therefore, the amount of chloride ions added as a result of the Purified Water EP is negligible relative to the total chloride in the finished drug substance.

It is our opinion, that Purified Water EP meets the requirement of "suitable quality" as discussed in the draft FDA guidance "Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients".

Thank you for your prompt response to this request for an opinion. If you need any further information, please give me a call.

G. Swetland

Sam Swetland

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Table 1

Comparison of USP and EP Specifications for Purified Water						
Test	**USP 23**	**USP 23 Suppl. 5**	**USP 23 Suppl. 7**	**USP 23 Suppl. 8**	**EP 1997**	**EP 7/1/1999**
pH	Yes	Yes	Yes	Removed	Yes	Removed
Chloride	Yes	Removed	Removed	Removed	Yes	Removed
Sulfate	Yes	Removed	Removed	Removed	Yes	Removed
Limits of Ammonia	Yes	Removed	Removed	Removed	Yes	Removed
Calcium	Yes	Removed	Removed	Removed	N/A	N/A
Calcium and Magnesium	N/A	N/A	N/A	N/A	Yes	Removed
Carbon Dioxide	Yes	Removed	Removed	Removed	Not Specified	Not Specified
Heavy Metals	Yes	Removed	Removed	Removed	Yes	Yes
Aluminum	Not Specified	Not Specified	Not Specified	Not Specified	Yes	For Dialysis Use Only
Nitrates	Not Specified	Not Specified	Not Specified	Not Specified	Yes	Yes
TOC	Not Specified	< 0.5 mg/L or use	< 0.5 mg/L	< 0.5 mg/L	Not Specified	< 0.5 mg/L or use
Oxidizable Substances	Yes	Oxidizable Substances	Removed	Removed	Yes	Oxidizable Substances
Total Solids	Yes	Removed	Removed	Removed	Yes	Removed
Conductivity	Not Specified	< 1.1 µS/cm @ 20°C)	< 1.1 µS/cm @ 20°C	< 1.1 µS/cm @ 20°C	Not Specified	< 4.3 µS/cm @ 20°C
Microbial Contamination	Not Specified	Not Specified	Not Specified	Not Specified	NMT 10^2 Org/mL	NMT 100 Org/mL
Bacterial Endotoxins	Not Specified	Not Specified	Not Specified	Not Specified	For Dialysis Use Only	For Dialysis Use Only

Purified water

The committee of Public Health (Partial Agreement) CD-P-SP (resolution AP/CSP (99) 1) has decided to fix by July 1st 1999 the date when the States Parts to the Convention of European Pharmacopoeia will have to put into practice the monograph « Purified water » approved by the European commission of Pharmacopoeia during the November 1998 Session.

Reference : PA/PH/Exp. 3/T (98) 106 DEF

PURIFIED WATER

H_2O M_r 18,02

DEFINITION

The purified water is set aside for the preparation of medicine other than the ones which should be sterile and pyrogen free, apart from an justified and authorised exception.

Purified water in bulk

PRODUCTION

The purified water in bulk is prepared by distillation, by exchange of ions or by any other appropriate process from water set aside for human consumption as established by the competent Authority.

During the production and conservation, appropriate measures are taken to assure that the number of total viable aerobic germs is appropriately controlled and mastered. The alert and intervention level are established in order to detect any undesirable evolution. In normal conditions, a number of total viable aerobic germs (2.6.12) of 100 micro-organisms per millilitre, determined by filtration on membrane in using of the gelosed B area, is considered as appropriate intervention level. The volume of the sample is chosen according to the given result.

Furthermore, the test of total organic carbon (2.2.44) is done, with a limit of 0,5 mg/l, or the test according to the oxidisable substances : boil during 5 min. a mixture of 100 ml purified water, of 10 ml of diluted R sulphuric acid and of 0,1 ml of Potassium Permanganate 0,02 M. The solution remains slightly pink coloured.

The conductivity (2.2.38) is also controlled (maximum 4,3 $\mu S\ cm^{-1}$ at 20 °C).

The purified water in bulk is conserved and distributed in conditions that avoid the growth of micro-organisms and any other contamination.

CHARACTERS

Limpid liquid, colourless, odourless and tasteless.

TEST

Nitrates. *In a test tube placed in frozen water, introduce 5 ml of purified water in bulk* and add 0,4 ml of Potassium chloride R solution at 100 g/l, 0,1 ml of Diphenylamin R solution, drop by drop in stirring, 5 ml of sulphuric acid azote free R. *Place the tube in* baln-marie at 50 °C. If, after 15 min, it appears a blue coloration, it is not more intense than the one of a simultaneously prepared witness and in the same conditions with a mixture of 4,5 ml water exempt of Nitrate R and 0,5 ml of 2 ppm solution of Nitrate (NO_3) R (0,2 ppm).

Heavy metals (2.4.8). In a glass bottle, heat in baln-marie 200 ml of purified water in bulk until reduction of volume to 20 ml. 12 ml of the concentrated solution satisfy the limit A test of heavy metals (0,1 ppm). Prepare the witness with 10 ml of solution at 1 ppm of lead (Pb) R.

Aluminium (2.4.17). The purified water in bulk is set aside for the preparation of *solutions for dialyse satisfying* the test of *Aluminium*. To 400 ml of purified water in bulk, add 10 ml of Acetate solution pH 6,0 R and 100 ml of distilled water R. The solution satisfies at the limit test of *Aluminium* (10 µg/l). *Use as reference solution a* mixture of 2 ml of 2 ppm of Aluminium solution (Al) R, of 10 ml of Acetate solution pH 6,0 R and 98 ml of distilled water R and as blank solution a mixture of 10 ml of Acetate solution pH 6,0 R and 100 ml of distilled water R.

Bacterial endotoxines (2.6.14). If the purified water in bulk is set aside for the preparation of solution for dialyse without any other appropriate process of elimination of bacterial endotoxines, the limit concentration in endotoxines is 0,25 U.I. by millilitre.

LABELLING

The label indicates, in the appropriate cases, that the substance is convenient to the preparation of solutions for dialyse.

Examinée dans des conditions appropriées de visibilité, l'eau stérilisée pour préparations injectables est limpide et incolore.

Chaque récipient contient une quantité d'eau suffisante pour permettre le prélèvement du volume nominal.

ESSAI

L'eau stérilisée pour préparations injectables satisfait aux essais prescrits dans la section « Eau purifiée conditionnée en récipients » de la monographie *Eau purifiée (0008)*, avec modification des essais « Acidité ou alcalinité », « Substances oxydables », « Chlorures » (dans le cas des récipients de volume nominal inférieur ou égal à 100 ml) et « Résidu à l'évaporation ». Elle satisfait en outre aux essais « Contamination particulaire », « Stérilité » et « Endotoxines bactériennes ».

Acidité ou alcalinité. A 20 ml d'eau stérilisée pour préparations injectables, ajoutez 0,05 ml de *solution de rouge de phénol R*. Si la solution est colorée en jaune, elle vire au rouge en présence de 0,1 ml d'*hydroxyde de sodium 0,01 M*. Si la solution est colorée en rouge, elle vire au jaune en présence de 0,15 ml d'*acide chlorhydrique 0,01 M*.

Conductivité (*2.2.38*). Dans le cas des récipients de volume nominal inférieur ou égal à 10 ml, la conductivité n'est pas supérieure à 25 $\mu S \cdot cm^{-1}$. Dans le cas des récipients de volume nominal supérieur à 10 ml, la conductivité n'est pas supérieure à 5 $\mu S \cdot cm^{-1}$.

Substances oxydables. Portez à ébullition 100 ml d'eau stérilisée pour préparations injectables avec 10 ml d'*acide sulfurique dilué R*. Ajoutez 0,2 ml de *permanganate de potassium 0,02 M* et portez à ébullition pendant 5 min. La solution reste légèrement colorée en rose.

Chlorures (*2.4.4*). Dans le cas des récipients de volume nominal inférieur ou égal à 100 ml, 15 ml d'eau stérilisée pour préparations injectables satisfont à l'essai limite des chlorures (0,5 ppm). Préparez le témoin avec un mélange de 1,5 ml de *solution à 5 ppm de chlorure (Cl) R* et de 13,5 ml d'*eau R*. Examinez les solutions dans l'axe vertical des tubes.

Résidu à l'évaporation. Evaporez à siccité, au bain-marie, 100 ml d'eau stérilisée pour préparations injectables puis desséchez le résidu à l'étuve à 100-105 °C. Dans le cas des récipients de volume nominal inférieur ou égal à 10 ml, la masse du résidu n'est pas supérieure à 4 mg (0,004 pour cent). Dans le cas des récipients de volume nominal supérieur à 10 ml, la masse du résidu n'est pas supérieure à 3 mg (0,003 pour cent).

Contamination particulaire : particules non visibles (*2.9.19*). L'eau stérilisée pour préparations injectables satisfait, selon le cas, à l'essai A ou à l'essai B.

Stérilité (*2.6.1*). L'eau stérilisée pour préparations injectables satisfait à l'essai de stérilité.

Endotoxines bactériennes (*2.6.14*). La concentration limite en endotoxines est de 0,25 U.I. par millilitre.

• Eau purifiée

Le Comité de Santé Publique (Accord Partiel) CD-P-SP (résolution AP/CSP (99) 1) a décidé de fixer au 1er juillet 1999 la date à laquelle les Etats Parties à la Convention de la Pharmacopée Européenne devront mettre en application la monographie « Eau purifiée » adoptée par la Commission Européenne de Pharmacopée lors de sa Session de novembre 1998.

[redacted]

EAU PURIFIÉE

Aqua purificata

H_2O M_r 18,02

DÉFINITION

L'eau purifiée est une eau destinée à la préparation de médicaments autres que ceux qui doivent être stériles et exempts de pyrogènes, sauf exception justifiée et autorisée.

Eau purifiée en vrac

PRODUCTION

L'eau purifiée en vrac est préparée par distillation, par échange d'ions ou par tout autre procédé approprié à partir d'une eau destinée à la consommation humaine comme établi par l'Autorité compétente.

Au cours de la production et de la conservation, des mesures appropriées sont prises pour garantir que le nombre de germes aérobies viables totaux est convenablement contrôlé et maîtrisé. Des seuils d'alerte et d'intervention sont établis en vue de la détection de toute évolution indésirable. Dans des conditions normales est considéré comme seuil d'intervention approprié un nombre de germes aérobies viables totaux (*2.6.12*) de

100 microorganismes par millilitre, déterminé par filtration sur membrane en utilisant du milieu gélosé B. Le volume de l'échantillon est choisi en fonction du résultat attendu.

En outre l'essai du carbone organique total (*2.2.44*) est effectué, avec une limite de 0,5 mg/l, ou bien l'essai suivant des substances oxydables : chauffez à ébullition pendant 5 min un mélange de 100 ml d'eau purifiée, de 10 ml d'*acide sulfurique dilué R* et de 0,1 ml de *permanganate de potassium 0,02 M*. La solution reste légèrement colorée en rose.

La conductivité (*2.2.38*) est également contrôlée (au maximum 4,3 $\mu S \cdot cm^{-1}$ à 20 °C).

L'eau purifiée en vrac est conservée et distribuée dans des conditions visant à empêcher la croissance de microorganismes et à éviter toute autre contamination.

CARACTÈRES

Liquide limpide, incolore, inodore et insipide.

ESSAI

Nitrates. Dans un tube à essai placé dans de l'eau glacée, introduisez 5 ml d'eau purifiée en vrac et ajoutez 0,4 ml d'une solution de *chlorure de potassium R* à 100 g/l, 0,1 ml de *solution de diphénylamine R* puis, goutte à goutte et en agitant, 5 ml d'*acide sulfurique exempt d'azote R*. Placez le tube dans un bain-marie à 50 °C. Si, après 15 min, il apparaît une coloration bleue, elle n'est pas plus intense que celle d'un témoin préparé simultanément et dans les mêmes conditions avec un mélange de 4,5 ml d'*eau exempte de nitrate R* et de 0,5 ml de *solution à 2 ppm de nitrate (NO_3) R* (0,2 ppm).

Métaux lourds (*2.4.8*). Dans une capsule de verre, chauffez au bain-marie 200 ml d'eau purifiée en vrac jusqu'à réduction du volume à 20 ml. 12 ml de la solution concentrée satisfont à l'essai limite A des métaux lourds (0,1 ppm). Préparez le témoin avec 10 ml de *solution à 1 ppm de plomb (Pb) R*.

Aluminium (*2.4.17*). L'eau purifiée en vrac destinée à la préparation de solutions pour dialyse satisfait à l'essai de l'aluminium. A 400 ml d'eau purifiée en vrac, ajoutez 10 ml de *solution tampon acétate pH 6,0 R* et 100 ml d'*eau distillée R*. La solution satisfait à l'essai limite de l'aluminium (10 µg/l). Utilisez comme solution de référence un mélange de 2 ml de *solution à 2 ppm d'aluminium (Al) R*, de 10 ml de *solution tampon acétate pH 6,0 R* et de 98 ml d'*eau distillée R* et comme solution à blanc un mélange de 10 ml de *solution tampon acétate pH 6,0 R* et de 100 ml d'*eau distillée R*.

Endotoxines bactériennes (*2.6.14*). Si l'eau purifiée en vrac est destinée à la préparation de solutions pour dialyse sans autre procédé approprié d'élimination des endotoxines bactériennes, la concentration limite en endotoxines est de 0,25 U.I. par millilitre.

ÉTIQUETAGE

L'étiquette indique, dans les cas appropriés, que la substance convient à la préparation de solutions pour dialyse.

Eau purifiée conditionnée en récipients

L'eau purifiée conditionnée en récipients est de l'eau purifiée en vrac répartie en récipients et conservée dans des conditions visant à assurer la qualité microbiologique requise. Elle est exempte de tout additif.

CARACTÈRES

Liquide limpide, incolore, inodore et insipide.

ESSAI

L'eau purifiée conditionnée en récipients satisfait aux essais prescrits dans la section « Eau purifiée en vrac » ainsi qu'aux essais complémentaires suivants :

Acidité ou alcalinité. A 10 ml d'eau purifiée conditionnée en récipients, récemment bouillie puis refroidie dans un flacon de verre borosilicaté, ajoutez 0,05 ml de *solution de rouge de méthyle R*. La solution ne se colore pas en rouge.

A 10 ml d'eau purifiée conditionnée en récipients, ajoutez 0,1 ml de *solution de bleu de bromothymol R1*. La solution ne se colore pas en bleu.

Substances oxydables. Chauffez à ébullition pendant 5 min un mélange de 100 ml d'eau purifiée conditionnée en récipients, de 10 ml d'*acide sulfurique dilué R* et de 0,1 ml de *permanganate de potassium 0,02 M*. La solution reste légèrement colorée en rose.

Chlorures. A 10 ml d'eau purifiée conditionnée en récipients, ajoutez 1 ml d'*acide nitrique dilué R* et 0,2 ml de *solution de nitrate d'argent R2*. L'aspect de la solution ne présente aucun changement pendant 15 min au moins.

Sulfates. A 10 ml d'eau purifiée conditionnée en récipients, ajoutez 0,1 ml d'*acide chlorhydrique dilué R* et 0,1 ml de *solution de chlorure de baryum R1*. L'aspect de la solution ne présente aucun changement pendant 1 h au moins.

Ammonium. A 20 ml d'eau purifiée conditionnée en récipients, ajoutez 1 ml de *solution alcaline de tétraiodomercurate de potassium R*. Après 5 min, examinez la solution suivant l'axe vertical du tube. La solution n'est pas plus fortement colorée qu'une solution témoin préparée simultanément par addition de 1 ml de *solution alcaline de tétraiodomercurate de potassium R* à un mélange de 4 ml de *solution à 1 ppm d'ammoniaque (NH_4) R* et de 16 ml d'*eau exempte d'ammonium R* (0,2 ppm).

Redacted 1

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secret and/or

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commercial

information

ORIGINAL

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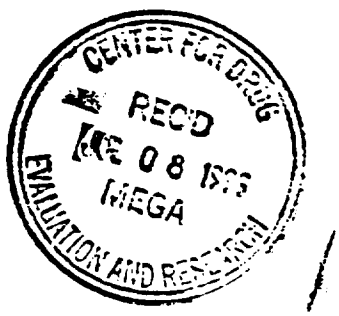
GUIDELINES INCORPORATED

July 7, 1999

NEW CORRES

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: Notification of Intent to File an Amendment - New Drug Application for Levulan® Kerastick™ (aminolevulinic acid HCl) for Topical Solution, 20% - **NDA No. 20-965**

Dear Dr. Wilkin:

On behalf of our client, DUSA Pharmaceuticals, Inc., and in accordance with 21CFR §314.110, we herewith notify the Agency of DUSA's intent to file an amendment to the subject application responding to the Agency's correspondence dated June 27, 1999. We are pleased to receive an Approvable letter for the above referenced NDA. DUSA is reviewing the Agency's proposed labeling modifications and may request further clarification from the Agency. Additionally, DUSA is working with the drug substance manufacturer to implement the proposed corrective actions in order to assure a satisfactory GMP inspection. Currently, the drug substance manufacturer anticipates completing the necessary modifications and documentation by the end of August 1999 and is expected to be ready for re-inspection in September 1999. In the interim, DUSA will submit a complete amendment responding to all items listed in your letter dated June 27, 1999. If you need any further information, please feel free to contact me at (954) 433-7480.

No action initiated
7/21/99

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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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds

DUSA\Final NDA Documents\Cover Letter-23.doc

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BI

GUIDELINES INCORPORATED

ORIG AMENDMENT

June 2, 1999

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 the Sponsor's response to the Microbiologist's List of Deficiencies which was provided via Facsimile Transmission dated 5 May, 1999. In this communication, the microbiologist requested that a Microbial Limits Test be performed on the constituted finished product and that such testing should be conducted soon after mixing, in line with the recommended time limit for usage of the product.

DUSA Pharmaceuticals' accepts the reviewer's comments and commits to perform a Microbial Limits Test on each lot of finished product in accordance with the USP methodology, <61> Microbial Limits Test. Furthermore, DUSA accepts the reviewer's specifications of a total aerobic count of [redacted] CFU/mL and an absence of [redacted] and is proposing a total yeast and mold count of [redacted] CFU/mL. These recommendations have been incorporated into the finished product specification that was provided in the initial NDA submission as Table B.26. The revised specification is provided in Attachment 1.

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The microbiological testing of the finished product will be conducted at a contract microbiological testing facility. The facility [redacted] is a FDA registered microbiological testing facility located in [redacted]
The complete name, address and FDA registration number of the testing facility are provided in Attachment 2.

We trust that this information adequately responds to the Microbiologist's comments. If you need any further information, 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,

S. Swetland

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
Enclosure: Revised Finished Product Specifications and Test Lab

DUSA\Final NDA Documents\Cover Letter-22.doc

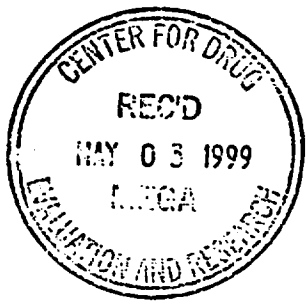
APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

ORIGINAL

BM

April 30, 1999



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 information requested during a phone conversation between Ms. Olga Cintron and myself on 13 April 1999. During this phone call, Ms. Cintron indicated that the device operating instructions utilized in the Phase III clinical trials made reference to the use of a chin rest to provide support for the patient's head during the treatment. Ms. Cintron mentioned that the medical reviewer wanted to know the frequency of the use of the chin rest in the clinical trials.

The DUSA Chin Rest was provided to each Phase III clinical site as an optional accessory to be used at the physician's discretion. Other means of providing support for the patient's head for the duration of the light treatment were allowed.

A retrospective evaluation was conducted by DUSA Pharmaceuticals to estimate the percentage of patients who utilized the chin rest supplied by DUSA and what percentage of patients used other means of head support during the light treatment. This retrospective evaluation was conducted as a survey of the

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Phase III clinical sites by means of a questionnaire that was completed by each site. A copy of the questionnaire is provided in Attachment 1.

Based on the responses of the clinical sites (15 of 16 sites responded), greater than 50% of the patients in the Phase III studies used the chin rest supplied by DUSA. Additionally, greater than 25% of the patients used other means of head support such as an examination table, a chair with headrest, or a table with a pillow. At least 7% of the patients used no head support during the light treatment. There is no data available for 6% of the patients (site did not respond to questionnaire). A tabulation of the results of the questionnaire, by protocol and by center, is provided in Attachment 2.

As discussed in previous phone conversations with both Ms. Cintron and Mr. Richard Felten of CDRH, DUSA agrees to include wording in the operating instructions for the commercial device that states that "A chin rest, available from DUSA, may be used to provide support for the patient's head during treatment." This label statement is similar to the statement used in the device operating instructions provided for the Phase III clinical trials.

Accordingly, concurrent with this submission, DUSA is submitting a PMA Amendment to the PMA application for DUSA's Blu-U Blue Light Photodynamic Therapy Illuminator (PMA No. P990019) providing device design and manufacturing information for the chin rest used in the Phase III clinical trials and revised operating instructions for the clinical device. A desk copy of the PMA Amendment will be provided to Olga Cintron.

We trust that this information has adequately responded to the medical reviewer's questions. If you need any further information, 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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
Enclosure: Chin Rest Survey Results and Questionnaire

DUSA\NDA Documents\Cover Letter-20.doc

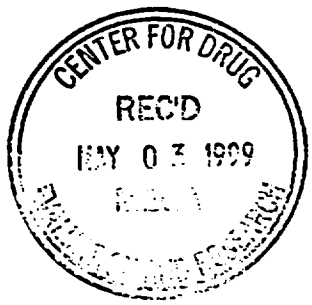
GUIDELINES INCORPORATED

ORIGINAL

NEW CORRESP

NC

April 30, 1999



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

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

Dear Dr. Wilkin:

On behalf of our client, DUSA Pharmaceuticals, Inc., we herewith submit to the Agency the published case report of Gniazadowska et al **[1]**, which came to our attention during routine Medline Searches following the submission of DUSA Pharmaceuticals, Inc. NDA for Levulan® Kerastick™ 20% (NDA No. 20-965). It is the first and only paper we are aware of in the world literature which reports apparent contact dermatitis in a patient treated with topical 5-aminolevulinic acid (ALA) + light. A copy of the article is provided in Attachment 1.

The patient is a 54 year old woman whose previous history of skin reactions was remarkable only for occasional eczema on the face, forearms and hands. This was thought to be related to occupational exposure to cosmetics during her work as a saleswoman in a perfumery. She was treated with photodynamic therapy (PDT) using topical ALA for Bowen's disease of the vulva using as topical therapy a gel containing 2 g of ALA, 8 mL of propylene glycol, 0.2 g of silicic acid, and 2 mL of aqueous sodium bicarbonate (8.4%). The gel was applied to the lesion for 6 h, after which the area was exposed to 100 J/cm2 635 nm laser light

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(Coherent GmbH). Immediately following laser light exposure the treated area appeared erythematous and was covered with a sterile, dry, nonadherent dressing. By the following day, an intensely itchy, papuloerythematous dermatitis had developed in the genital region, spreading to the groin, abdomen, buttocks, and medial thighs. The skin lesions cleared after several days of topical corticosteroids.

Patch tests were performed 10 weeks after clearing of the acute dermatitis. Using Finn Chambers® on Scanpor®, the following compounds were tested: a standard series (German Contact Dermatitis Research Group), a series of common vehicles and preservatives of topical preparations, the original ALA gel, and its individual constituents. Reading of the test reactions was carried out after 2 and 3 days. Exposure of the test area to light was avoided until the end of the test procedure. The patient showed positive patch test reactions to colophony, fragrance mix, the ALA gel as a whole, and to a 20% aqueous solution of ALA. The most exuberant reactions were noted on day 3 to fragrance mix and to the ALA solution. Control patch tests with the ALA gel were negative in 10 subjects.

The authors point out that since the interval between administration of the ALA gel and the occurrence of the dermatitis was only 1 day, the patient had likely acquired sensitization earlier as a result of contact with ALA, ALA derivatives or other compounds of similar chemical structure. However, they were not able to identify the source of sensitization from the medical history of the patient.

Commentary:

This report of apparent contact dermatitis in a patient treated with topical ALA in a gel formulation is of interest due to the apparent pre-sensitization of the patient to ALA, judging from her rapid reaction (within 24 hours) after PDT.

DUSA Pharmaceuticals, Inc. has treated over 600 patients using topical Levulan (aminolevulinic acid HCl) in 3 different formulations plus light since the inception of clinical studies under IND #[redacted] an oil-in-water emulsion (cream) vehicle, an ointment preparation, and a solution formulation. Levulan concentrations have been tested from 2% to 30%. The number of patients treated using each Levulan formulation are listed in the Table:

Table Showing Patients Treated with Topical Levulan® Formulations

Levulan Formulation	% Levulan Tested	Number of patients tested	Maximum number of applications/patient	Reports of contact dermatitis.
Levulan Solution	2.5, 5, 10, 20, 30	460	2	0
Levulan Cream	2, 10, 20, 30	114	4[1]	0
Levulan Ointment	2.5, 5, 10, 20	43	30	0
Total	-	617	-	0

[1]2 patients received 6 exposures, 1 patient received 7 exposures and 1 patient received 15 exposures.

The most often-repeated exposures to topical Levulan + light occurred in protocol ALA-006. In that protocol 17 patients were treated with Levulan in ointment formulation together with blue light in multiple treatments for PDT of plaque psoriasis. Patients received at least one patch test to determine minimal light dose phototoxicity, and then received up to 30 consecutive treatments of Levulan in ointment formulation + blue light as twice or thrice weekly treatments.

No incidences of contact dermatitis were reported with any formulation of topical Levulan in any DUSA Pharmaceuticals, Inc. study.

In the most recent comprehensive review articles of published clinical studies using topical ALA PDT **[2, 3]**, 92 patients are described as having been treated for a number of indications, including AKs (n = 10), Bowen's disease (n = 17), and basal cell carcinoma (n = 65) **[2]**. Contact dermatitis was not listed among the adverse events reported in published studies discussed in either review article.

Although contact dermatitis cannot be ruled out as a possible adverse event of topical Levulan PDT treatment in the future, it is apparent that the patient and therapy described in the case report of Gniazadowska et al **[1]** differs in several ways from those in DUSA-sponsored or in published reports of other clinical trials:

1. The patient appears to have been pre-sensitized to ALA or a related molecule, possibly from prior occupational exposure.

2. In the case report ALA was formulated as a gel rather than a cream, ointment or solution as it has been formulated in the great majority of reported studies. The formulation may affect sensitization.

3. The anatomical site of treatment in this case report (vulvar skin) may be more predisposed to sensitization than other cutaneous sites.

It is DUSA Pharmaceuticals, Inc. opinion and direct experience that the Levulan topical solution formulation used in the majority of clinical trials, and recently applied for marketing approval in NDA No. 20-965, is unlikely to cause allergic contact dermatitis.

We trust that this information has adequately responded to the medical reviewer's questions. If you need any further information, 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

SDS/sds
Enclosure: Contact Dermatitis Article

DUSA\NDA Documents\Cover Letter-21.doc

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

ORIGINAL

April 26, 1999

ORIG AMENDMENT

BMI

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 information requested by the medical officer in a Facsimile Transmission dated 9 April 1999. The requested information is provided below by request.

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

   A review of the case report forms for clinical studies ALA-018 and ALA-019 revealed that a total of 5 patients had target lesions located on the ears. These 5 patients (18115, 18118, 18401, 18402, 18407) were enrolled in ALA-018. No patients in ALA-019 had lesions treated on the ears.

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2. **If any target lesions were located on patients' ears, were patients' whose target lesions were located on their ears among the patients with face lesions, or among the patients with scalp lesions?**

All 5 patients who had lesions treated on the ears received facial treatments. No patients with scalp treatments had target lesions located on the ears.

3. **How many target lesions were located on patients' ears?**

There were 6 target lesions located on the patients' ears. Three of these lesions were treated with Levulan 20% and 10J/cm² Blue Light and 3 were treated with Vehicle and 10J/cm² Blue Light.

4. **What was the lesion clearance rate for target lesions located on patients' ears?**

The complete response rate for lesions treated on patients' ears is summarized below for clinical studies ALA-018, ALA-019 and ALA-018/019.

COMPLETE RESPONSE RATE FOR LESIONS LOCATED ON PATIENTS' EARS
Studies ALA-018, ALA-019 & ALA-018/019

	ALA-018		ALA-019		ALA-018/019	
	No. Lesions	(%)	No. Lesions	(%)	No. Lesions	(%)
Total No. Lesions on Ear Treated with Levulan 20% and 10 J/cm² Blue Light[1]	3		0		3	
Lesion Complete Response Rate						
Week 8[2]	2/3	(67)	–		2/3	(67)
Week 12	3/3	(100)	–		3/3	(100)
Total No. Lesions on Ear Treated with Vehicle and 10 J/cm² Blue Light	3		0		3	
Lesion Complete Response Rate						
Week 8[2]	0/3	(0)	–		0/3	(0)
Week 12	0/3	(0)	–		0/3	(0)

[1]Treated with Levulan 20% Solution and 10 J/cm² of blue light delivered at 10 mW/cm².
[2]Lesions not exhibiting a complete response at Week 8 could have been retreated.

If you need any further information regarding these requests, 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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSA\NDA Documents\Cover Letter-19.doc

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

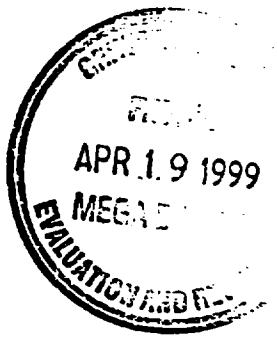
ORIG AMENDMENT

BL

16 April 1999

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

ORIGINAL



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 information requested in a phone conversation between Olga Cintron of your Division and myself. During that phone conversation, the Agency requested copies of the photographs or artwork that would be used in the Levulan Kerastick activation instructions in the "Dosage and Administration" section of the proposed Package Insert.

Enclosed as requested, please find four copies of the proposed Package Insert for the Levulan Kerastick. This draft labeling is the same as the Package Insert submitted in the original NDA Application (Revision: June 1998) except for the following:

1. On page 12 of the labeling, the "picture text boxes" have been replaced with digital photographs to show the activation steps for the Levulan Kerastick. These photographs are "concept proofs" and may not be the actual photographs that will be used in the final labeling.
2. On page 14 of the labeling, the "Revision" has been changed to April 16, 1999 to reflect the new revision date.

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

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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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

Enclosure:
Levulan Kerastick Proposed Package Insert

SDS/sds
DUSA \ Final NDA Documents \ Cover Letter-17.doc

GUIDELINES INCORPORATED

ORIGINAL

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15 March 1999

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

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

Dear Dr. Wilkin:

The purpose of this correspondence is to provide the Agency with DUSA Pharmaceuticals' agreement and comments regarding a proposed administrative change in NDA number 20-965 for Levulan Kerastick Topical Solution. This change was recommended by the Agency during a phone conversation on Thursday March 4, 1999 between Olga Cintron of CDER's Division of Dermatological and Dental Drug Products, Richard Felten of CDRH's Division of General and Restorative Devices and, on behalf of DUSA Pharmaceuticals, Inc., Sam Swetland of Guidelines, Inc.

In this phone conversation the Agency advised DUSA Pharmaceuticals that it had decided that the device information for this drug/device combination product, originally submitted under the NDA, would be transferred to a PMA application under the administration of the CDRH, and was seeking the sponsor's comments and concerns.

DUSA agrees with the proposed administrative change and bases its agreement on the following understandings as discussed during the above phone conversation or presented here.

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1. The device information that is already submitted in the NDA for the Model 4170 and all review information applicable to the device will be assigned a PMA number by CDRH.

2. The CDRH will send out a standard Acknowledgment Letter informing DUSA of the PMA number and list the receipt date of the PMA as the original date of NDA receipt.

3. Upon completion of CDRH's administrative review, an Approvable Letter will be issued since the review and site inspections have already been completed. The Approvable Letter will state that the approval of the PMA is dependent upon CDER's review and approval of the NDA.

4. Once CDER issues an approval letter, CDRH will issue a similar letter approving the PMA.

5. As the sponsor, DUSA Pharmaceuticals will maintain ownership and regulatory responsibility for both the NDA and the PMA applications.

6. Once the device is approved as a PMA, manufacturers of similar devices will not be able to gain approval without DUSA's permission to cross-reference it's clinical database contained in the NDA, or without conducting their own clinical studies to justify the safety and efficacy of the combination drug/device therapy.

7. Information to support approval of the commercial device will be submitted to the PMA in second quarter 1999. This submission will be reviewed and approved as a PMA Amendment if it is received in time to complete the review prior to CDER's decision to approve the NDA. If the review cannot be completed before the approval of the NDA, the PMA Amendment for the commercial device will be withdrawn and resubmitted as a PMA Supplement to the approved clinical device PMA.

If any of these understandings are incorrect or if other significant issues should be considered, please call me at (954) 433-7480.

Sincerely,

Samuel D. Swetland

Samuel D. Swetland
Vice President,
Regulatory Affairs and Compliance

SDS/sds
DUSA\AK NDA\Final NDA Documents\Cover Letter and TOC\Cover Letter-16.doc

APPEARS THIS WAY
ON ORIGINAL

GUIDELINES INCORPORATED

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ORIG AMENDMENT
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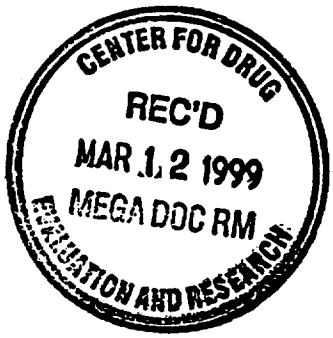

11 March 1999

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 tne 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.

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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

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

GUIDELINES INCORPORATED

26 February 1999

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ORIGINAL

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

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

Dear Dr. Wilkin:

The above referenced New Drug Application describes a drug/device combination therapy and includes information on the medical device as well as the drug substance and drug product. As agreed to during the Pre-NDA discussions, the original application described the design and manufacture of the Model 4170 Blue Light Photodynamic Therapy Illuminator that was used in DUSA Pharmaceuticals' Phase III clinical trials. The original NDA submission also indicated that DUSA would provide information covering the design and manufacture of the commercial version of the device, the Model 4170 Blue Light Photodynamic Therapy Illuminator (Blu-U™), in a NDA Amendment in February 1999. However, due to unforeseen delays in obtaining injection molded components, production of the Model 4170 has been delayed. As a result, complete manufacturing documentation is not yet available. It is anticipated that these delays will postpone submission of the NDA Amendment covering the Model 4170 into the second quarter of 1999.

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The design modifications incorporated into the commercial device, the Model 4170, will improve the manufacturability, enhance the aesthetic appeal, and decrease service needs. The Model 4170 will meet all of the same optical and performance specifications as the Model 4170 [redacted] all optically active components are the same for both units. Documentation substantiating the optical performance equivalence of the 4170 [redacted] and the 4170 will be included as part of the Amendment.

If you need any further information regarding this submission, 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,

Samuel D. Swetland
Vice President,
Regulatory Affairs and Compliance

SDS/sds
DUSAVAK NDA\Final NDA Documents\Cover Letter and TOC\Cover Letter-13.doc

APPEARS THIS WAY
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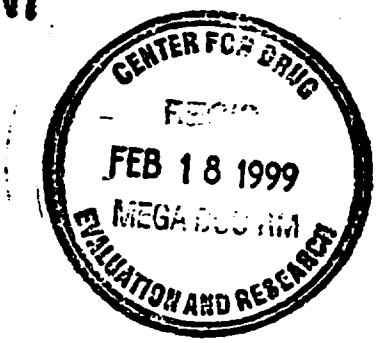
NDA ORIG AMENDMENT

BM

February 17, 1999



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 information requested by the medical officer in Facsimile Transmissions dated 05 January 1999 and 01 February 1999. The information provided in this submission is summarized below.

January 05, 1999 correspondence:

1. The medical officer requested that the sponsor confirm the reviewer's tabulation and analysis of the cutaneous adverse events for the ALA-018 clinical study and to perform an analogous analysis of the cutaneous adverse events for the other pivotal clinical trial (ALA-019). This information is provided in Attachments 1 and 2 for studies ALA-018 and ALA-019, respectively. Please note that DUSA was not able to confirm the reviewer's analysis in every instance. Therefore, DUSA has provided their analyses, performed as requested in the correspondence of January 05, 1999 and clarified in a correspondence dated January 11, 1999, and has included an explanation of the criteria used to perform these analyses. Furthermore, for the reviewer's ease, electronic copies of these tables are provided in the attached Diskette (Archival Copy only).

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2. The reviewer requested that the sponsor provide the names of the unblinded investigators who participated in the clinical studies ALA-018 and ALA-019. Attachment 3 contains a list of the primary unblinded investigator(s), by center number, for both studies ALA-018 and ALA-019.

February 01, 1999 correspondence:

1. The medical officer requested the clinical slides for patients 18102, 18103, 18106, 18116, 18117, 18216, 18221, 18301, 18302, 18501, 18510, and 18608. All clinical slides for the above patients are provided in Attachment 4 of the Archival Copy only.

If you need any further information regarding these documents, 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:
Diskette
Attachment 1-4

SDS/sds
DUSA\NDA Documents\Cover Letter-11.doc

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DUPLICATE

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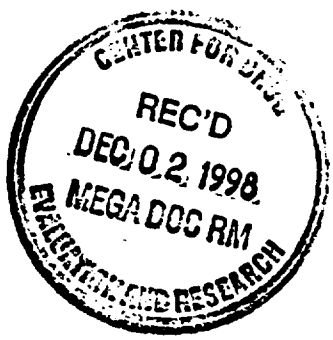

December 1, 1998

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: 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 30 November 1998 between Olga Cintron of your Division and Sam Swetland of Guidelines, Inc.

As per our discussion, electronic copies of the draft labeling for the package insert, Kerastick applicator and medical device were requested to aid in the review of the application labeling. The requested files are provided as detailed below.

Diskette Title	File Name	File Description
Draft Product Labeling	Package Insert 6-98.doc	Draft Package Insert
	Kerastick Labels 6-98.doc	Draft Levulan® Kerastick™ Carton labeling (cartons of 1, 4, 6, and 12 applicators) and Applicator label
	Device Labels 6-98.doc	Draft Device labels and Operation Instructions for Commercial Device

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Regarding the device labeling, please note that this application contains information on the 4170 Blue Light Photodynamic Therapy Illuminator (Model 4170 that was used in the Phase III clinical trials. To facilitate review of the product labeling for the Levulan Kerastick, draft labeling for the proposed commercial device, the 4170 Photodynamic Therapy Illuminator (Model 4170, trade name: Blu-U™) was provided in the draft labeling section of the NDA. However, changes in the device labeling are anticipated since the details of the 4170 commercial design had not been completed at the time of the NDA submission. Modifications to the light source design are to facilitate commercial manufacture and will not substantially affect the principles of operation of the device. Therefore, the electronic draft labeling provided in this submission is the proposed draft labeling for the commercial device (model 4170) as submitted in the NDA, not the labeling for the clinical devices (model 4170 which was also provided in the NDA.

If you need any further information regarding these documents, please feel free to contact me.

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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

Enclosure:
1 Diskette – Draft Product Labeling

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DUSA\NDA Documents\Cover Letter-10.doc

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PPLICATION 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	DATE OF SUBMISSION
DUSA Pharmaceuticals, Inc.	December 1, 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
Phone: (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)*	PROPRIETARY NAME *(trade name)* IF ANY
Aminolevulinic Agid HCl	Levulan® Kerastick

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5-amino-4-oxopentanoic acid	5-ALA HCl, 5-ALA, ALA

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	20%	Topical

(PROPOSED) INDICATION(S) FOR USE:

Treatment of actinic keratoses of the face and scalp

APPLICATION 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: Response to Information Request - Phone call - 11/30/98

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — 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

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

See Attachment to Form FDA 356h

ATTACHMENT TO FORM FDA 356h

ESTABLISHMENT INFORMATION:

Drug Substance

The drug substance will be manufactured, packaged, controlled and shipped by [redacted] the drug substance manufacturer. Stability studies of the drug substance will be conducted by [redacted]

Name and Address of Manufacturing Site: [redacted]

Establishment Registration No.: Not Applicable

Contact Person and Phone No.: [redacted]

Site Inspection by FDA: The facility is ready for inspection.

Drug Product

The drug product will be manufactured, packaged, labeled, controlled and shipped by North Safety Products, the drug product manufacturer. North Safety Products will be responsible for the manufacture of the bulk solution vehicle, filling and sealing of the glass ampules and assembly of the Levulan Kerastick. North Safety Products is responsible for the in-process testing of the bulk Levulan Topical Solution Vehicle.

Name and Address of the Manufacturing Site:

North Safety Products
2000 Plainfield Pike
Cranston, RI 02921

Establishment Registration No.: #1217998

Contact Person and Phone No.: Jonny Smith
Manager, Business Quality
(401)-946-4400

Site Inspection by FDA: This facility is ready for inspection.

The raw materials, process intermediates and finished products are analyzed by a contract analytical laboratory. The finished product stability studies are also conducted by the contract laboratory listed below:

Guidelines Analytical Laboratories, Inc. (GAL)
10320 USA Today WAY
Miramar, FL 33025
DMF No

Establishment Registration No.: #1052961

Contact Person and Phone No.: Mike Ray
President
(954)-433-7480

Site Inspection by FDA: This facility is ready for inspection.

CROSS REFERENCES:

DUSA's IND for Aminolevulinic Acid HCl: IND #
GAL's DMF: DMF #:
DMF: DMF#
DMF: DMF #:
DMF: DMF #

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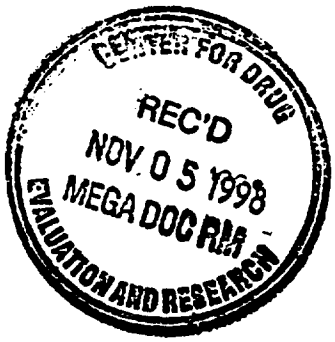

November 4, 1998

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: 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 23 October 1998 between Olga Cintron of your Division and Ishrat Nasirullah of Guidelines, Inc.

As per our discussion, the Medical Officer requested electronic copies of the Phase III Medical Reports and any other medical reports that are available electronically. The requested files are provided as detailed below.

Diskette Title	File Name	File Description
Protocol ALA-019	ALA-019 Report.doc	Medical Report Text for Protocol ALA-019
	ALA-019 Summary Tables.doc	Medical Report Summary Tables for Protocol ALA-019
Protocol ALA-018	ALA-018 Report.doc	Medical Report Text for Protocol ALA-018
	ALA-018 Summary Tables.doc	Medical Report Summary Tables for Protocol ALA-018
Protocol ALA-017	ALA-017 Report.doc	Medical Report Text for Protocol ALA-017
Protocol ALA-007/ALA-016	ALA-007 Report.doc	Medical Report Text for Protocol ALA-007
	ALA-016 Report.doc	Medical Report Text for Protocol ALA-016

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Please note that the medical report summary tables are printed from SAS files for the original medical report. For ease of use by the reviewer, we have provided these files as text files in MS-Word 7.0 format. Therefore, the font size and spacing may differ slightly from the printed version that was previously submitted, but the data has not been changed. Additionally, since this reformatting takes a considerable amount of time, the summary tables for the Phase II studies have not been included in order to provide the Phase III files and the Phase II medical report text in a timely manner. However, if after review of the above files the Medical Officer needs the summary tables for the Phase II studies, we will convert the Phase II files and provide them as soon as possible.

If you need any further information regarding these documents, please feel free to contact me.

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

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance

SDS/sds
DUSA\NDA Documents\Cover Letter-9.doc

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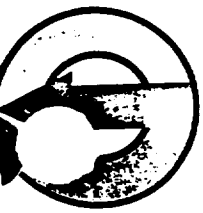
NDA ORIG AMENDMENT ORIGINAL



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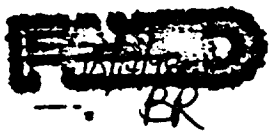
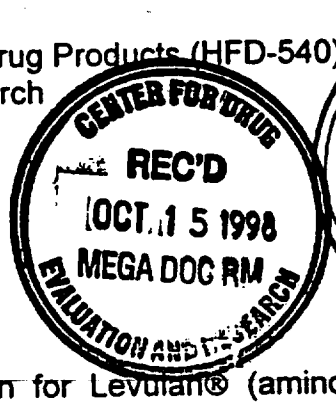
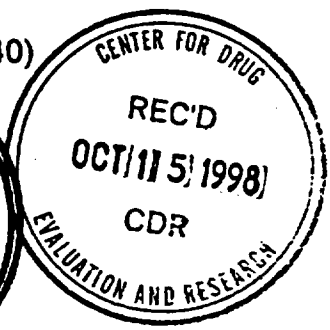


October 14, 1998

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 13 October 1998 between Olga Cintron of your Division and Sam Swetland of Guidelines, Inc.

The attached tables, which are taken from the NDA Application Summary, summarize the non-clinical studies provided as part of the Levulan Kerastick NDA. Of these studies, the Acute Dermal Toxicology Study in Rabbits, [redacted] 6703-100 (Vol. 1.5.6, p. 5-1713) listed in Table F.3, utilized the proposed market formulation. The other studies utilized investigational formulations appropriate for the route of administration to be evaluated in that particular non-clinical protocol. I trust that this clarifies the matter for the pharmacologist. If you need any further information regarding these formulations, please feel free to contact me.

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