APPLICATION NUMBER:  20-965

CHEMISTRY REVIEW(S)
DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-965 CHEM. REVIEW #: 1 REVIEW DATE: 10-JUN-1998

SUBMISSION/TYPEDOCUMENT DATE CDER DATE ASSIGNED DATE

NAME & ADDRESS OF APPLICANT:
DUSA Pharmaceuticals, Inc.
400 Columbus Avenue
Valhalla, NY 10595

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

DRUG PRODUCT NAME
Proprietary: LEVULAN®
Nonproprietary/USAN: aminolevulinic acid hydrochloride
Code Names/#'s: ALA, 5-ALA, 5-ALA HCl, S-
Chemical Type:
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of actinic keratoses in conjunction with a blue light illuminating device.

DOSAGE FORM:
Solid for topical solution
STRENGTHS:
20%
ROUTE OF ADMINISTRATION:
Topical
DISPENSED: _X_ Rx _______ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

\[
\begin{align*}
\text{Chemical Name:} & \quad 5\text{-aminolevulinic acid hydrochloride} \\
\text{Mol. Formula:} & \quad C_9H_8NO_4\cdot HCl \\
\text{Mol. Weight:} & \quad 167.59 \\
\text{CAS No.} & \quad [5451-09-2] \\
\text{Melting Pt.:} & \quad 151-156^\circ C \text{ (decomp.)} \\
\text{pH (aq.):} & \quad 1.77 (1:5 aqueous solution) \\
\text{pK}_a & \quad 3.816 \\
\text{Solubilities:} & \quad \text{freely soluble in water; slightly soluble in methanol, ethanol; practically insoluble in chloroform, hexane, mineral oil.}
\end{align*}
\]

SUPPORTING DOCUMENTS:
DMF ______ Type II, __________________________ authorized by letter dated 29-JUN-1998; for the manufacture of 5-amino-levulinic acid hydrochloride. This DMF has been reviewed in conjunction with this NDA and found to be adequate. The sponsor provided all pertinent
NDA 20-965
DUSA Pharmaceuticals
LEVULAN® KERASTICK™ for Topical Solution, 20%

chemistry, manufacturing and control data pertaining to the drug
substance in the DMF.

DMF Type III, letter dated June 14, 1996,
signed by for the manufacture of tubular containers
made from:

DMF Type III, authorized by letter dated
12-APR-1996, signed by for the manufacture of Low Density Polyethylene resin.

DMF Type I, Guidelines Analytical Laboratories, Inc., authorized
by letter dated 29-JUN-1998, signed by Sam Swetland; for the
facilities, personnel and procedures used by this contract lab and
agent.

RELATED DOCUMENTS:
Patents:
IND for 5-ALA solution, 10%; active in HFD-540.

The following patents are claimed for the drug or method of use of the
drug:

U.S. Patent No. 5,079,262, expiration date 28-JUL-2009, owned by
Queens University at Kingston and assigned exclusively to DUSA
Pharmaceuticals, Inc. for method of use of LEVULAN for topical
treatment of actinic keratoses.

U.S. Patent No. 5,211,938, expiration date 18-MAY-2010, owned by
Queens University at Kingston and assigned exclusively to DUSA
Pharmaceuticals, Inc. for method of use of LEVULAN for topical
treatment of actinic keratoses.

U.S. Patent No. 5,422,093, expiration date 28-JUL-2009, owned by
Queens University at Kingston and assigned exclusively to DUSA
Pharmaceuticals, Inc. for method of use of LEVULAN for topical
treatment of actinic keratoses.

Appendices:
1. Manufacturing process flowchart, 7 pages.
2. Applicator tip schematic drawing, 1 page.
3. Microbiology consultation reviews, 11 pages.
5. Draft carton and applicator labels, 9 pages.
7. Investigational formulation and clinical trial summary tables, 5
   pages.
8. Report from Joint Pre-approval inspection, 15 pages.

CONSULTS:

The proposed trade name "LEVULAN KERASTICK" was submitted to the
Labeling and Nomenclature Committee (LNC) on 04-JUN-1999 through
Chairman Dan Boring, Ph.D. (HFD-530).
NDA 20-965
DUSA Pharmaceuticals
LEVULAN® KERASTICK™ for Topical Solution, 20%

CONCLUSIONS & RECOMMENDATIONS:

Based on the review of the chemistry, manufacturing and controls information presented in the NDA, and the inspections of the manufacturing facilities, a recommendation of "Not Approvable" is made.

J. S. Hathaway, Ph.D.
Review Chemist

cc: Orig. NDA 20-965 (with all appendices)
HPD-540/DivisionFile (with all appendices)

cc: With Appendices 1 and 2 only:
HPD-540/Chem/JSHathaway
HPD-540/ChemTeamLdr/WHDeCamp
HPD-540/DivDir/JWilkin
HPD-830/DivDir/CWChen
HPD-540/MedOffr/MOKun
HPD-540/PharmTox/LReidd
HPD-540/ProjMgr/OCintron
HPD-805/Micro/PCooney
HPD-805/Micro/BRiley
HPD-/BioPharm/DBashaw

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/[S/ 6/12/99

[APPEARS THIS WAY ON ORIGINAL]
DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
HFD-540
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-965

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Therapeutic Class: 1 S

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![Chemical Structure](attachment:image.png)

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Mol. Formula: C₅H₉NO₂.HCl
Mol. Weight: 167.59
CAS No.: [5451-09-2]
NDA 20-965
DUSA Pharmaceuticals
LEVULAN® KERASTICK™ for Topical Solution, 20%

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PH (aq.): 1.77 (1:5 aqueous solution)
pKa: 3.816

SUPPORTING DOCUMENTS:
DMF Type II [ ] authorized by letter dated 29-JUN-1998; for the manufacture of 5-amino-levulinic acid hydrochloride.

REMARKS
Amendments and correspondence covered in this review were received as follows:
7/29/99: Comparison of USP and EP specifications for Purified Water
10/15/99: Amendment of DMF [ ]
11/12/99: Revision of package insert

CONCLUSIONS & RECOMMENDATIONS:
Based on the review of the chemistry, manufacturing and controls information presented in the NDA and the subsequent amendments listed above, a recommendation of "Approval" is made.

/ S /
J. S. Hathaway, Ph.D.
Review Chemist

cc: Orig. NDA 20-965
HFD-540/DivisionFile
HFD-540/Chem/JSHathaway
HFD-540/ChemTeamLdr/WHDeCamp [S]/12/2/99
HFD-540/DivDir/JWilkin
HFD-830/DivDir/CWChen
HFD-540/MedOffr/MOKun [S]/12/2/99
HFD-540/PharmTox/LReid
HFD-540/ProjMgr/OCintron
HFD-805/Micro/PCooney
HFD-805/Micro/BRiley
HFD-/BioPharm/DBashaw

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