CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY LABELING REVIEW
CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

NDA#: 50-741 **REVIEW #**: 1 **COMPLETED DATE**: 08/29/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Major Amendment (AZ)	03/03/00	05/16/00	05/18/00

NAME AND ADDRESS OF APPLICANT:

Stiefel Laboratories, Inc.
255 Alhambra Circle, Suite 1000
Coral Gables, Florida 33134

CONTACT PERSON:

William A. Carr, Jr.
Vice President
Route 145,
Oak Hill, New York 12460
Tel: (518) 239-6901

DRUG PRODUCT NAME:

Proprietary: Clindoxyl™ Gel (clindamycin phosphate / benzoyl peroxide)
Non-Proprietary: clindamycin phosphate / benzoyl peroxide
USAN: Clindamycin Phosphate, USP / Benzoyl Peroxide, USP
CAS No: *CAS-24729-96-22 / CAS-94-36-0*

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. W.T.:

Clindamycin phosphate:

Chemical Name/Structure = See 2000 USAN (page 173)
Molecular Formula = $C_{18}H_{34}ClN_2O_8PS$
Molecular Weight = 504.96

Benzoyl peroxide:

Chemical Name/Structure = See 2000 USAN (page 83)
Molecular Formula = $C_{14}H_{10}O_4$
Molecular Weight = 242.23

PHARMACOLOGICAL CATEGORY / INDICATION(s):

Clindamycin phosphate is a semi-synthetic lincomycin antibiotic drug. Benzoyl peroxide is an antibacterial and keratolytic agent.

According to the Applicant's Package Insert labeling: The drug product is indicated in the topical treatment of acne vulgaris.

DOSAGE FORM: Gel
STRENGTH: Clindamycin phosphate equivalent to 1% (10 mg/g) clindamycin and 5% (50 mg/g) benzoyl peroxide.
ROUTE OF ADMINISTRATION: Topical (dermatologic use)
DOSAGE / DURATION:

Clindoxyl™ Gel is applied once daily in the evening, or as directed by a physician.

DISPENSED: Rx

CONSULTS:

The Division of Dermatologic and Dental Drug Products (DDDDP / HFD-540) only requested a microbiology review on the **CLINICAL PHARMACOLOGY – Microbiology** labeling portion of the Package Insert.

REMARKS:

The "major amendment" resubmission is the Applicant's response to the Agency on the "not approvable" communications dated May 14 1997 and January 30, 1998. The resubmission also includes the Applicant's response to a February 20, 1998 telephone communication (on the deficiencies and corrective actions) and a March 1998 (draft) communication (restating the deficiencies and corrective actions) on NDA 50-741.

CONCLUSIONS:

At this time, there is no microbiology review on the **CLINICAL PHARMACOLOGY – Microbiology** labeling portion of the Package Insert.

DDDDP (HFD-540) is recommending "non-approval" on NDA 50-741, Clindoxyl™ Gel (clindamycin phosphate equivalent to 1% clindamycin and 5% benzoyl peroxide). The "non-approval" action is due to the clinical studies not demonstrating that Clindoxyl™ Gel is superior in effectiveness to its component benzoyl peroxide (see Medical Officer's Review of Amendment to NDA 50-741 Resubmission – Major Amendment, dated June 26, 2000). Therefore, no review on the Package Insert labeling is being initiated.

/S/

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 50-741
540/Division File
HFD-540/DivDir/JWilkin
HFD-520/Micro/HVSilver
HFD-540/TLMO/SWalker
HFD-540/MO/PHuene
HFD-540/ProjMgr/OCintron
HFD-520/Rev. by HVS:
Filename: 50741FIN.doc
DDDDP: NON-APPROVAL (NA)

Concurrence Only:
HFD-520/DepDvDir/Lgavrilovich 11/21/00
HFD-520/TLMicro/ATSheldon 11/17/00
R.D. and Final Initialed 11/17/00 A.E.P.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

Clinical Microbiology Labeling Review

CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

NDA#: 50-741 **REVIEW #**: 2 **COMPLETED DATE**: 07/24/02

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	02/22/02	02/26/02	07/18/02

NAME AND ADDRESS OF APPLICANT:

Stiefel Laboratories, Inc.
255 Alhambra Circle, Suite 1000
Coral Gables, Florida 33134

CONTACT PERSON:

William A. Carr, Jr.
Vice President
Route 145,
Oak Hill, New York 12460
Tel: (518) 239-6901

DRUG PRODUCT NAME:

Proprietary: Clindoxyl™ Gel (clindamycin phosphate / benzoyl peroxide)
Non-Proprietary: clindamycin phosphate / benzoyl peroxide
USAN: Clindamycin Phosphate, USP / Benzoyl Peroxide, USP
CAS No: CAS-24729-96-22 / CAS-94-36-0

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL. W.T.:

Clindamycin phosphate:

Chemical Name/Structure = See 2000 USAN (page 173)
Molecular Formula = $C_{18}H_{34}ClN_2O_8PS$
Molecular Weight = 504.96

Benzoyl peroxide:

Chemical Name/Structure = See 2000 USAN (page 83)
Molecular Formula = $C_{14}H_{10}O_4$
Molecular Weight = 242.23

PHARMACOLOGICAL CATEGORY / INDICATION(s):

Clindamycin phosphate is a semi-synthetic lincomycin antibiotic drug. Benzoyl peroxide is an antibacterial and keratolytic agent.

According to the previous Applicant's package insert labeling: The drug product is indicated "for the topical treatment of acne vulgaris".

DOSAGE FORM: Gel
STRENGTH: Clindamycin phosphate equivalent to 1% (10 mg/g) clindamycin and 5% (50 mg/g) benzoyl peroxide.
ROUTE OF ADMINISTRATION: Topical (dermatologic use)
DOSAGE AND ADMINISTRATION (according to the Applicant's label):

"Clindoxyl Topical Gel should be applied once daily, in the evening or as directed by the physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry."

DISPENSED: Rx

CONSULTS:

The Division of Dermatologic and Dental Drug Products (DDDDP / HFD-540) requested a microbiology review on the **CLINICAL PHARMACOLOGY – Microbiology** labeling portion of the package insert.

REMARKS:

The amendment is the Applicant's response to the Agency's 09/06/00 "not approvable" letter.

The Applicant submitted additional clinical data; however, no microbiology studies were conducted in the clinical trials with this drug product. Also, the proposed claimed indication was changed from "for the topical treatment of acne vulgaris" to "for the topical treatment of inflammatory acne vulgaris".

DDDDP / HFD-540 requested a review on the microbiology portion of the labeling in the package insert. Therefore, an evaluation will be on this NDA for content and format of the microbiology section of the package insert only. The content will be based on available information in the submission and available published literature.

CONCLUSIONS:

From the microbiological perspective, an "approval" letter should be issued to the Applicant after negotiations of the revised draft labeling in the **Microbiology** portion of the labeling, respectively, as explained on pages 3 and 4 and finalized on pages 4 and 5.

LABELING

Presently, DDDDP / HFD-540 is updating the dermatologic microbiology portion of the labeling in package inserts using the following 4 described subsections: **Mechanism of Action**, ***In Vitro* Activity**, ***In Vivo* Activity**, and **Drug Resistance**. Therefore, the **Microbiology** portion of the

Clindoxyl™ Gel (clindamycin phosphate / benzoyl peroxide) labeling is described as follows:

– The Applicant submitted the following described **Microbiology** labeling portion of the package insert:

"**Microbiology:** The clindamycin and benzoyl peroxide components individually have been shown to have in vitro activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product."

– Clinical Microbiologist's Comments:

After discussions and concurrence between this Clinical Microbiology Reviewer and DDDDP / HFD-540 on 07/22/02, the **Microbiology** labeling portion of the package insert is revised (double-underlined = _____) and described as follows:

Microbiology:

Mechanism of Action

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis[1]. Benzoyl peroxide is a potent oxidizing agent[2].

***In Vivo* Activity**

No microbiology studies were conducted in the clinical trials with this product.

***In Vitro* Activity**

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product and is not known.

Drug Resistance

There are reports of an increase of *P. acnes* resistance to clindamycin in the treatment of acne[3,4,5,6]. In patients with *P. acnes* resistant to clindamycin the clindamycin component of this product may provide no additional benefit beyond benzoyl peroxide alone.

REFERENCES

1. Murray, P.R., E.J. Baron, M.A. Pfaller, F.C. Tenover, and R.H. Yolken. 1999. *Manual of CLINICAL MICROBIOLOGY.* American Society for Microbiology. 7th ed. **115**:1486.

2. Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A.G. Gilman. 1996. Goodman &

Gillman's, *The PHARMACOLOGICAL BASIS OF THERAPEUTICS.* McGraw-Hill. 9th ed. **64**:1605.

3. Cove, J. 2002. *Acne and antibiotic resistance.* IBMS Manchester Bacteriology Discussion Group meeting on March 12, 2002.

4. Nord, C.E. 2001. *Antibiotic treatment in patients with severe acne causes development of antibiotic resistance.* 101st General Meeting of the American Society of Microbiology, Orlando, FL. Session 220/C, Paper C-325.

5. Callen, J.P., and A. W. Lucky. 2001. *Acne. Best Practice of Medicine* > Dermatology. [ICD-9CM code 706.1, 706.]

6. Pirouzi, M.A., and P. Pirouzi. 1998. *ACNE VULGARIS AND OTHER ACNEIFORM ERUPTIONS.* The Canadian Atlas of Dermatology.

CONCLUSIONS/RECOMMENDATIONS on the LABELING for NDA 50-741

From the microbiological perspective, an "approval" letter should be issued to the Applicant after negotiations of the revised marked "draft" labeling on the Microbiology portions, respectively. The labeling on NDA 50-741, Clindoxyl™ Gel (clindamycin phosphate / benzoyl peroxide), is revised to read as described:

Microbiology:

Mechanism of Action

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Benzoyl peroxide is a potent oxidizing agent.

***In Vivo* Activity**

No microbiology studies were conducted in the clinical trials with this product.

***In Vitro* Activity**

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product and is not known.

Drug Resistance

There are reports of an increase of *P. acnes* resistance to clindamycin in the treatment of acne. In patients with *P. acnes* resistant to clindamycin the clindamycin component of this product may provide no additional benefit beyond benzoyl peroxide alone.

Harold V. Silver
Clinical Microbiology Reviewer
DAIDP/HFD-520

cc: Orig. NDA 50-741
HFD-540/Division File
HFD-540/DivDir/J.Wilkin
HFD-540/TLMO/M.Luke
HFD-540/MO/P.Huene
HFD-540/ProjMgr/V.L.Lutwak
HFD-520/Micro/H.V.Silver
Filename: N50741FIN.doc
APPROVAL (AP)

Concurrence Only:
HFD-520/TLMicro/ATSheldon
RD#1 & Final Initialed 7/24/02 ATS
HFD-520/DepDir/LGavrilovich

APPEARS THIS WAY
ON ORIGINAL

HFD-540
Clinkon

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 50-741
13 April 2000

APR 13 2000

A. 1. NDA 50-741
APPLICANT: Stiefel Laboratories, Inc.
255 Alhambra Circle
Suite 1000
Coral Gables, FL 33134

2. PRODUCT NAMES: Clindoxyl Gel (clindamycin phosphate and benzoyl peroxide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Topical cream for application to affected areas of the face.

4. METHODS OF STERILIZATION:
The product is a topical and as such is not a sterile preparation, but, conforms to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is intended for use in the treatment of acne vulgaris.

B. 1. DATE OF INITIAL SUBMISSION: 3 May 1996

2. DATE OF AMENDMENT (RESUBMISSION): 3 March 2000 (Subject of this Review).

3. RELATED DOCUMENTS: [redacted] [redacted] 1, [redacted]

4. ASSIGNED FOR REVIEW: 10 April 2000

C. REMARKS: The drug product is manufactured at:

Stiefel Research Laboratories, Inc.
Oak Hill, NY 12460

D. CONCLUSIONS: The application is recommended for approval on the basis of the microbial quality of the drug product.

/S/ 13 April 2000

Paul Stinavage, Ph.D.

FAC 4/13/00

cc: Original NDA 50-741
HFD-805/Stinavage/Consult File
HFD-540/Div File/O. Cintron

Drafted by: P. Stinavage, 13 April 2000
R/D initialed by P. Cooney,

APPEARS THIS WAY ON ORIGINAL

NDA 50-741 (Clindoxyl Gel) was reviewed for Microbiology concerns and resulted in a comment and a request for a commitment. The applicant responds to those questions/commitments in this submission. Each comment has been reprinted from the Microbiologist's Review #1 of NDA 50-741 in bolded, italicized print and is reviewed separately.

1. ***Please be aware that it is not possible to define the term "any other etiologic agent". The term, as written, encompasses a very large number of microorganisms. As written, it would not be possible to meet these criteria.***

The method "Microbial Quality of Nonsterile Products (BT-11)" term "any other etiologic agent" has been modified to include more definitive terminology.

Satisfactory

2. ***Antimicrobial preservative effectiveness testing should be performed on the first three production lots of product as part of the stability protocol. This testing should minimally be performed initially and at product expiry. Please provide a commitment to perform this testing.***

The applicant has committed to performing antimicrobial preservative effectiveness testing of the first three production lots.

Satisfactory

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

(Division/Office)			FROM:	
HFD-160 Peter Cooney			HFD-540 /S/	
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/7/00	—	50-741	A2	3/31/00
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG		DESIRED COMPLETION DATE
Clindoxy 1 Gel	—	~~B~~ 45		—

NAME OF FIRM: Steifel Laboratories

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)*

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

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY 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)*

Volume 15.2 contains information in response to microbiological issues described in the NA letter of 5-14-97. Volume 1 of this resubmission was forwarded to Dr. Paul Stinavage.

Please review for acceptability.

SIGNATURE	METHOD OF DELIVERY *(Check one)*
/S/	☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

STINAVAGE
NOV - 7 1996

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 50-741
7 November 1996

A. 1. NDA 50-741
APPLICANT: Stiefel Laboratories, Inc.
255 Alhambra Circle
Suite 1000
Coral Gables, FL 33134

2. PRODUCT NAMES: Clindoxyl® Gel (clindamycin phosphate and benzoyl peroxide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Topical cream for application to affected areas of the face.

4. METHODS OF STERILIZATION:
The product is a topical and as such is not a sterile preparation, but, conforms to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is intended for use in the treatment of acne vulgaris.

B. 1. DATE OF INITIAL SUBMISSION: 3 May 1996

2. DATE OF AMENDMENT: 19 June 1996

3. RELATED DOCUMENTS: —

4. ASSIGNED FOR REVIEW: 11 June 1996

C. REMARKS: The drug product is manufactured at:

Stiefel Research Laboratories, Inc.
Oak Hill, NY 12460

D. CONCLUSIONS: The application is approvable, pending the applicant's commitment to provide the data indicated in "E. Review Notes" and "Draft of Letter to Applicant" post-approval.

/S/ 7 November 1996
Paul Stinavage, Ph.D.
11/7/96

cc: Original NDA 50-741
HFD-805/Stinavage/Consult File
HFD-540/Div File/K.D. White

Drafted by: P. Stinavage, 7 November 1996
R/D initialed by P. Cooney

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages