CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-145

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS JUL 26 2000
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-145 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 7/26/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	
ORIGINAL	9/24/99	9/28/99	10/5/99	, Rev. 1
AMENDMENT/NC	1/24/00	1/28/00	2/15/00	
AMENDMENT/BL	3/02/00	3/06/00	3/16/00	
AMENDMENT/NC	3/28/00	4/04/00	4/11/00	
AMENDMENT/BC	5/01/00	5/09/00	5/15/00	
AMENDMENT/BL	6/05/00	6/07/00	6/18/00	
AMENDMENT/BL	7/06/00	7/10/00	7/13/00	
AMENDMENT/BC	7/24/00	7/25/00	7/26/00	

NAME & ADDRESS OF APPLICANT: Westwood-Squibb Colton Holding Partnership
100 Forest Avenue
Buffalo, New York 14213-1091

DRUG PRODUCT NAME

Proprietary: Vaniqa

Nonproprietary/USAN: eflornithine hydrochloride; D,L-2-(Difluoromethyl) ornithine monohydrochloride monohydrate

Code Names/#'s: BMS 203522;G-46

Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Ornithine Decarboxylase Inhibitor
Excessive Facial Hair in Women

DOSAGE FORM: Cream
STRENGTHS: 15%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: x Rx _____ OTC

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

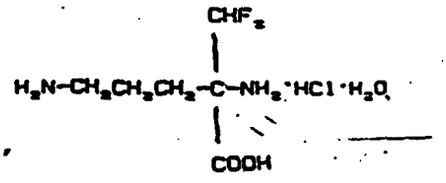
eflornithine hydrochloride (USAN) $C_6H_{12}N_2O_2F_2 \cdot HCl \cdot H_2O$

(±)-2-(difluoromethyl)ornithine hydrochloride monohydrate

a.w. 236.65

CAS Registry No. 96020-91-6 (67037-37-0, eflornithine)

other names and codes used: MDL 71,782A; RMI 71,782A; α-DFMO; α-difluoromethyl ornithine hydrochloride



Supporting Documents:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Reviewed	4/21/00	6/8/00
DMF			Reviewed	4/20/00	6/8/00
DMF			Under Review		

RELATED DOCUMENTS (if applicable):

IND

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NDA

NDA 19,879, Ornidyl (eflornithine HCl),i.v., Merrell Dow Research Institute

CONSULTS:

The project manager requested labeling consult on 2/17/00 to OPDRA.

REMARKS/COMMENTS:

The original NDA was found deficient in several areas of the CMC section. These CMC deficiencies were conveyed to them on 6/23/00 via fax (see Chemist's Review #1 dated 7/7/00 for "Draft of Chemist's Portion of Letter to Applicant"). In this regard, the applicant responded to these deficiencies with their amendment to the NDA dated 7/6/00. The review of the applicant's response is discussed in detail under the chemistry review notes below.

In addition, during a telecon on 6/7/00 with the applicant, the reviewer requested the lower detection limits for assay methods ——————— (see review notes below).

The labeling remains acceptable from a technical standpoint with the exception that the label claim of 15 % for Vaniqa cream is not accurately described. In this regard, the labeled strength of 15 % eflornithine HCl monohydrate corresponds to 13.9 % as the actual strength of the ——————— molecule (see page 19 of chemistry review notes for calculations). The applicant's response on 7/11/00 (via Fax) for a labeling revision to reflect the above change is unacceptable. Therefore, the applicant was requested to revise their labeling (PI, carton, and package) to reflect this change (see telecon dated 7/18/00).

In addition, the applicant submitted an amendment dated 7/11/00 to withdraw Humacao, PR as an additional manufacturing site for the drug product. This withdrawal is the result of a request made by the chemist on 6/28/00 to withdraw the Humacao, PR facility since it was too late to request an EER of this facility before the target date action letter (see telecon dated 6/28/00). The applicant was advised that they could submit a supplement requesting the Humacao, PR, facility after the approval of the NDA.

Furthermore, the applicant's amendment dated 7/24/00 requested a categorical exclusion from submitting an environmental assessment as required by 21 CFR 25.32(b).

After reviewing the data submitted in the NDA, the FDA requested on 7/24/00 that this categorical exclusion be submitted. In this regard, the data revealed that the entry of active moiety into the aquatic environment was less than 1 part per billion.

Methods Validation is pending; to be initiated as soon as possible.

CONCLUSIONS & RECOMMENDATIONS:

The NDA remains approvable from a manufacturing and controls standpoint. The labeling also remains approvable from a technical standpoint with the exception that the label claim of 15 % for Vaniqa cream is not accurately described. In this regard, the labeled strength of 15 % eflornithine HCl monohydrate corresponds to 13.9 % as the actual strength of the ——— molecule (see chemistry review notes for calculations). The applicant was informed of the labeling strength discrepancy and has therefore revised the label claim to 13.9 % (see 7/21/00 fax).

/S/ 7/26/00

Ernest G. Pappas, Review Chemist

cc: Orig. NDA 21-145
HFD-540/Division File
HFD-540/Pappas
HFD-540/Cook
HFD-540/Hill
HFD-805/Riley
HFD-540/Wright
HFD-540/Decamp
R/D Init by: Team Leader /S/ Sig WDC 7/26/2000

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JUL 1 1 2000

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

Addendum _

NDA #: 21-145 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 7/10/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/24/99	9/28/99	10/5/99
AMENDMENT/NC	1/24/00	1/28/00	2/15/00
AMENDMENT/BL	3/02/00	3/06/00	3/16/00
AMENDMENT/NC	3/28/00	4/04/00	4/11/00
AMENDMENT/BC	5/01/00	5/09/00	5/15/00
AMENDMENT/BL	6/05/00	6/07/00	6/18/00

NAME & ADDRESS OF APPLICANT: Westwood-Squibb Colton Holding Partnership
100 Forest Avenue
Buffalo, New York 14213-1091

DRUG PRODUCT NAME

Proprietary: Vaniqa

Nonproprietary/USAN: eflornithine hydrochloride; D,L-2-(Difluoromethyl)ornithine monohydrochloride monohydrate

Code Names/#'s: BMS 203522;G-46

Chem.Type/Ther.Class: **3 S**

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Ornithine Decarboxylase Inhibitor
Excessive Facial Hair in Women

DOSAGE FORM: Cream
STRENGTHS: 15%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __x__ **Rx** _____ **OTC**

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

See Chemist's Review #1

REMARKS/COMMENTS:

This is an addendum to Chemist's Review # 1 dated 6/29/00 for Eflornithine Hydrochloride 15% Cream. This addendum references the Methods Validation information that was requested via telecon on 7/9/00 with firm regarding additional information. In this regard, the firm was requested to update the Methods Validation report of the NDA (Vol. 1.5, pg. 90) to include all samples needed to perform the methods validation. This included all of the samples on pg. 90, including the impurity reference materials used in the methods.

CONCLUSIONS & RECOMMENDATIONS:

Methods Validation is pending, waiting on firm's resubmission of the new sample page to NDA. The Methods Validation will be initiated shortly afterwards.

The NDA remains approvable from a manufacturing and controls standpoint.

/S/ 7/10/00

Ernest G. Pappas,
Review Chemist

cc: Orig. NDA 21-145
HFD-540/Division File
HFD-540/Pappas
HFD-540/Cook
HFD-540/Hill
HFD-805/Riley
HFD-540/Wright
HFD-540/Decamp
R/D Init by: Team Leader /S/ 7/11/2000

/S/ 7/16/00

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JUL 7 2000

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-145 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/29/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/24/99	9/28/99	10/5/99
AMENDMENT/NC	1/24/00	1/28/00	2/15/00
AMENDMENT/BL	3/02/00	3/06/00	3/16/00
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AMENDMENT/BC	5/01/00	5/09/00	5/15/00
AMENDMENT/BL	6/05/00	6/07/00	6/18/00

NAME & ADDRESS OF APPLICANT: Westwood-Squibb Colton Holding Partnership
100 Forest Avenue
Buffalo, New York 14213-1091

DRUG PRODUCT NAME

Proprietary: Vaniqa
Nonproprietary/USAN: eflornithine hydrochloride; D,L-2-(Difluoromethyl)ornithine monohydrochloride monohydrate

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STRENGTHS: 15%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __x__ Rx _____ OTC

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

Structural Formula / Chemical Name:

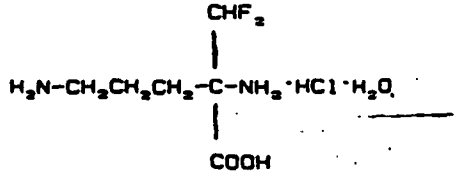
eflornithine hydrochloride (USAN) $C_6H_{12}N_2O_2F_2.HCl.H_2O$

(±)-2-(difluoromethyl)ornithine hydrochloride monohydrate

m.w. 236.65

CAS Registry No. 96020-91-6 (67037-37-0, eflornithine)

other names and codes used: MDL 71,782A; RMI 71,782A; α-DFMO; α-difluoromethyl ornithine hydrochloride



SUPPORTING DOCUMENTS:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Reviewed	4/21/00	6/8/00
DMF			Reviewed	4/20/00	6/8/00
DMF			Under Review		

RELATED DOCUMENTS (if applicable):

IND

IND

IND

IND

IND

IND

NDA

NDA 19,879, Ornidyl (eflornithine HCl),i.v., Merrell Dow Research Institute

CONSULTS:

The project manager requested labeling consult on 2/17/00 to OPDRA.

REMARKS/COMMENTS:

The applicant submitted a New Drug Application for Eflornithine Hydrochloride 15% Cream for the treatment of excessive female facial hair. This NDA has 3S classification.

Eflornithine HCl has been approved for the use in an intravenous route of administration under NDA 19-879. The CMC information was found acceptable for this NDA (see Chemist's Reviews # 1, 2 & 3, dated 3/7/89, 2/27/90, & 8/24/90).

In support of NDA 21-145, a comprehensive description of the CMC information was submitted for this drug product. Even though the CMC information was comprehensive, deficiencies remain in the areas of Manufacturing and Packaging, Specifications and Methods, and Stability. A Phase 4 commitment should be obtained from the applicant regarding

The applicant submitted an amendment dated 5/1/2000, which contained updated CMC information. This information included updated DMF information for the , a new facility at Humacao, PR to manufacture, package and test the drug product, change in lower pH specification, change in the of the sample tube, and change in the cartons for the 30 g and tubes. With the exception of a new site at Humacao, PR, the updated CMC information was found acceptable. However, the applicant should be requested to withdraw Humacao, PR as an additional plant site since this request came too late in the review process. See Chemist's review notes for information regarding these changes.

Furthermore, the applicant submitted additional amendments to update the NDA. These amendments were reviewed and are summarized as follows:

Amendment/NC dated 1/24/00- Proposed Pediatic Study Request; medical information; review not necessary for CMC; Sent to files as No Action Indicated.

Amendment/BL dated 3/2/00- Revised Draft Labeling; This labeling clarifies the language describing the indication and the summary of the overdosage information, note the new

address of the Westwood-Squibb business offices, and correct typographical errors in the tube and carton labeling. Action: Acceptable from technical standpoint.

Amendment/NC dated 3/28/00- General correspondence to request teleconference with FDA for the addition of Humacao, PR as a new manufacturing site; to discuss the updated ——— protocol in ——— Action: Send to files as NAI.

The applicant also submitted draft labeling with the original NDA; a minor correction in the storage temperature of the package insert should be made. This labeling was revised with their amendment dated 6/5/00. The labeling was reviewed and found acceptable from a technical standpoint (see Chemist's Review Notes).

Methods Validation is pending; to be initiated as soon as possible.

EER was found acceptable on 6/22/00 for ———, and Westwood Squibb Pharmaceuticals, Buffalo, NY ; see Memo from the Office of Compliance dated 6/26/00.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is found approvable from a manufacturing and controls standpoint. However, minor deficiencies in the CMCs remained. These CMC deficiencies should be conveyed to the applicant by IR letter or telecon.

/S/ 6/29/00

Ernest G. Pappas, Review Chemist

cc: Orig. NDA 21-145
HFD-540/Division File
HFD-540/Pappas
HFD-540/Cook
HFD-540/Hill
HFD-805/Riley
HFD-540/Wright
HFD-540/Decamp
R/D Init by: Team Leader 7/7/00

/S/

m.v. comment (pg. 40) must be revised in an addendum to reflect t'con of 7/5/00

(2) MW of active with monohydrate is 236.66, but should be based on MW without the monohydrate (= 218). The labeled conc. of active should be: (218.66)

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21145/000
Stamp: 27-SEP-1999 Regulatory Due: 27-JUL-2000
Applicant: WESTWOOD SQUIBB CLTN
100 FOREST AVE
BUFFALO, NY 142131091

Priority: 3S Org Code: 540
Action Goal: District Goal: 28-MAY-2000
Brand Name: VANIQA(EFLORNITHINE HCL)15%TOPICAL CREAM
Established Name:
Generic Name: EFLORNITHINE HCL
Dosage Form: CRM (CREAM)
Strength: 15%

FDA Contacts:
M. WRIGHT (HFD-540) 301-827-2084 , Project Manager
E. PAPPAS (HFD-540) 301-827-2066 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-JUN-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-APR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-NOV-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

Establishment: 1314666
WESTWOOD SQUIBB PHARMACEUT
100 FOREST AVE
BUFFALO, NY 14213
DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-JUN-2000
Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL