

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-145

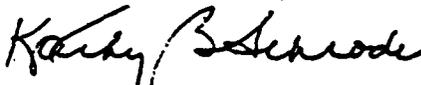
ADMINISTRATIVE DOCUMENTS

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Westwood-Squibb Colton Holdings Partnership 100 Forest Avenue Buffalo, New York 14213-1091		3. PRODUCT NAME efomithine hydrochloride 15% cream	
2. TELEPHONE NUMBER (Include Area Code) (716) 887-7680		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES" CHECK THE APPROPRIATE RESPONSE BELOW. <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).	
5. USER FEE I.D. NUMBER 3728		6. LICENSE NUMBER/ADA NUMBER N021-145	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (See Item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) <p style="text-align: center;">FOR BIOLOGICAL PRODUCTS ONLY</p> <input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92 <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box) <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (See Item 7, reverse side before checking box.) <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE FHS ACT			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See reverse side if answered YES)			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.			
Public reporting burden for this collection of information is estimated to average 30 minutes 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 (0910-0297) 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.	
Please DO NOT RETURN this form to this address.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Kathy B. Schrode, Ph.D. Director	DATE September 9, 1999

**SECTION 16
DEBARMENT CERTIFICATION**

SECTION 16 - DEBARMENT CERTIFICATION

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION

This certifies that Westwood-Squibb Colton Holdings Partnership has not used in any capacity any persons identified by the United States Food and Drug Administration on any Debarment List, or identified as having been permanently debarred by publication in the Federal Register since March 8, 1993.

Further, we certify that Westwood-Squibb Colton Holdings Partnership will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

We are not aware of any relevant convictions for which a person can be debarred as described in section 306 (a) and (b), for persons employed and/or affiliated with Westwood-Squibb Colton Holdings Partnership (including contractors) responsible for the development of data and information to support approval of this application for Eflornithine Hydrochloride 15% Cream.

Name	Kathy B. Schrode, Ph.D.
Title	Director
Date	September 9, 1999
Company	Westwood-Squibb Colton Holdings Partnership
Address	100 Forest Avenue
City	Buffalo, NY 14213
Telephone	(716) 887-7680

 9 Sep 99
Kathy B. Schrode, Ph.D. Director, Drug Regulatory Affairs

PATENT CERTIFICATION

Patent information and a declaration as required under 21 CFR §314.53 for new drug applications submitted under Section 505(b) of the Federal Food, Drug and Cosmetic Act is provided on the Patent Information page of this NDA. As noted under 21 CFR 314.50(i), patent certifications are required for Section 505 (b)(2) applications, and thus are not applicable to this NDA.

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ON ORIGINAL

PATENT INFORMATION

Westwood-Squibb Colton Holdings Partnership (the "Partnership") having an address at 777 Scudders Mill Road, Plainsboro, NJ 08536, is the applicant for NDA 21-145 covering efloornithine hydrochloride 15% cream for the indication: *treatment of excessive female facial hair*.

In accordance with the provisions of Section 505 (b) of the Federal Food, Drug and Cosmetic Act (the "Act") and 21 CFR §314.53, Westwood-Squibb Colton Holdings Partnership submits the following patent information for listing in the Food and Drug Administration's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Information called for by 21 CFR §314.53 (c)(1) and a declaration in accordance with 21 CFR §314.53 (c)(2) are provided below:

1. U. S. Patent No. 4,413,141, expiring November 1, 2000, is a composition of matter (compound) patent owned by Merrell Toraude et Cie., c/o Hoechst Marion Roussel, 10236 Marion Park, Kansas City, MO. This patent is listed in the Orange Book in connection with NDA 19,879 for the product Ornidyl sold by Hoechst Marion Roussel.
2. U. S. Patent No. 4,720,489, expiring January 19, 2005, is a method of use patent owned by The Gillette Company, and is under license to the Partnership, which is authorized to receive notice of patent certification under §§505(b)(3) and (j)(2)(B) of the Act and §§ 314.52 and 314.95.
3. U. S. Patent No. 5,648,394, expiring July 15, 2014, is a composition of matter (formulation)/ method of use patent owned by The Gillette Company, and is under license to the Partnership, which is authorized to receive notice of patent certification under §§505(b)(3) and (j)(2)(B) of the Act and 21 CFR §§314.52 and 314.95.

DECLARATION

The undersigned, in accordance with 21 CFR § 314.53(c) declares that United States Patent Nos. ~~4,413,141~~ 4,720,489, and 5,648,394 cover the composition, formulation and method of use of efloornithine 15% cream in the treatment of excessive female facial hair, the approval for which is being sought in this NDA.


Signature of the Authorized Person

Charles J. Zeller
Name of the Authorized Person

Associate Patent Counsel
Title of Authorized Person

Date: August 23, 1999

Trade Name: Vaniqa Cream, 13.9%

Generic Name : eflornithine hydrochloride

Applicant Name: Westwood-Squib Colton Holdings

HFD # 540

Approval Date If Known 7/27/00

JUL 26 2000

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES NO

b) Is it an effectiveness supplement?

YES NO

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-879

Ormidyl

2. Combination product

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

**APPEARS THIS WAY
ON ORIGINAL**

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

N/A

YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study Protocol DE140-001 (Double blind study)

Study Protocol DE140-002 (Double blind study)

Study Protocol DE140-010 (Open label study)

Study Protocol DE140-011 (Open label study)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

APPEARS THIS WAY
ON ORIGINAL

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #4	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study Protocol DE140-001 (Double blind study)
Study Protocol DE140-002 (Double blind study)
Study Protocol DE140-010 (Open label study)
Study Protocol DE140-011 (Open label study)

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES NO Explain:

Investigation #2

IND # YES NO Explain:

Investigation #3

IND # YES NO Explain:

Investigation #4

IND # YES NO Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

APPEARS THIS WAY
ON ORIGINAL

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

LSI - 7/25/00
Signature _____ Date _____
Title: Project Manager

LSI 7/26/00
Signature of ~~Office~~ _____ Date _____
Division Director

cc: Original NDA 21-145

Division File-540
HFD-540/Wright

HFD-93 Mary Ann Holovac

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ON ORIGINAL

11/25/00/WR/911

NDA 21-145

MAY 16 2000

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
Global Strategic Unit, Regulatory Sciences
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr. Schrode:

Reference is made to your correspondence dated January 24, 2000, requesting FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for VANIQA (eflornithine HCl cream) Cream, 15%.

We have reviewed your Proposed Pediatric Study Request and are unable to issue a Written Request on your submission at this time. No additional pediatric data are needed for the VANIQA (eflornithine HCl cream) Cream, 15%, to adequately label the product for use in the pediatric population 12 years of age and older. The NDA is still under review and a final action will occur at the conclusion of the review process.

If you have any questions, contact Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff, at 301 827-2020.

Sincerely,

JSJ 5/16/00

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 21-145
HFD 540 Division File
HFD 540/KozmaFornaro
HFD 540/Wright
HFD 540/Wilkin
HFD 540/Walker/5/11/00
HFD 540/Cook/5/11/00
HFD 104/D. Murphy
HFD 104/Roberts
HFD 104/T.Crescenzi
HFD 104/Locklear

Drafted: MJKF/5/15/00
Final: MJKF/5/15/00
Filename: 21145LSPEXC

LETTER SENT (LS)

/S/

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical investigators	<input checked="" type="checkbox"/> see attached	<input type="checkbox"/>
	<input checked="" type="checkbox"/> No disclosable information	<input type="checkbox"/>

- 2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- 3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dr. Sol I. Rajfer	Sr. V.P., WWC&D
FIRM/ORGANIZATION	
Bristol Myers Squibb Co.	
SIGNATURE	DATE
	9/13/99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and examining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address on the right.

Department of Health and Human Services
Food and Drug Administration
2400 Fishers Lane, Room 14C-03
Bethesda, MD 20857

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**SECTION 19
OTHER**

**SECTION 19 - OTHER - FINANCIAL DISCLOSURE BY CLINICAL
INVESTIGATORS**

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WITHHOLD 4 PAGE (S)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

APR 28 2000

DATE RECEIVED: 2/17/00

DUE DATE: 4/14/00

OPDRA CONSULT #: 00-0071

TO: Johnathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH:

Millie Wright,
Project Manager, DDDDP
HFD-540

PRODUCT NAME:
Vaniqa
(eflornithine HCl cream)
15%

MANUFACTURER: Westwood-Squibb Colton Holdings
Partnership

NDA: 21-145

SAFETY EVALUATOR: Peter Tam, RPh.

PDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Vaniqa. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

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4/28/00

151

4/28/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 4/17/00
NDA#: 21-145
NAME OF DRUG: Vaniqa
(eflornithine HCl cream)
15%
NDA HOLDER: Westwood-Squibb Colton Holdings Partnership

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) on February 17, 2000, to review the proposed proprietary drug name, Vaniqa, in regard to potential name confusion with existing proprietary/generic drug names.

PRODUCT INFORMATION

Vaniqa is a cream containing 15% eflornithine hydrochloride, an amino acid analog, for topical dermatological use in the treatment of excessive facial hair.

Eflornithine hydrochloride irreversibly inhibits the enzyme ornithine decarboxylase in vitro and in vivo. This enzyme is integral in the synthesis of polyamines. Data indicate that inhibition of ornithine decarboxylase inhibits cell division and synthetic functions, which affects the rate of hair growth. Vaniqa Cream has been shown to reduce the rate of growth in non-clinical and clinical studies.

Vaniqa is indicated for the treatment of excessive facial hair in women. It is used twice daily at least 8 hours apart or as directed by a physician.

Vaniqa Cream will be supplied in — 30 gm — plastic tubes.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or look alike to Vaniqa to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The panel discussion was conducted on 3/13/00 to gather professional opinions on the safety of the proprietary name, Vaniqa. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. There were only minor concerns from the panel on an existing approved drug name, Viagra, because of sound-alike and look-alike similarity. In general, the expert panel did not have any problem with this proposed name.

2. DDMAC

DDMAC has no objections.

Product Name	Dosage form(s) / Generic name	Usual Dose	Observation
Vaniqa	Topical cream efloornimic 15(3)1.5%	Apply to face and neck area bid	
Viagra	25,50,100 mg, sildenafil tablets	50 mg taken as needed	*SA/LA

*SA = Sound-alike

*LA = Look-alike

¹ MICROMEDEX Healthcare Internet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

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B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Vaniqa with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Vaniqa (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

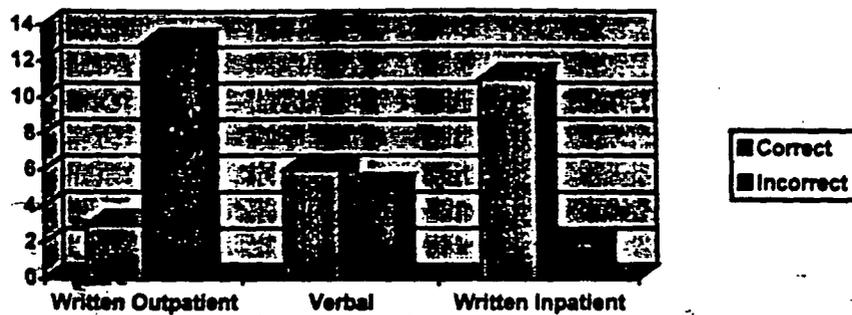
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> Vaniqa #1 As directed	Vaniqa #1 As directed
<u>Inpatient RX</u> Continue Vaniqa as directed	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	31	16 (52%)	3	13
Verbal	32	11 (34%)	6	5
Written Inpatient	31	13 (42%)	11	2
Total	94	40 (43%)	20 (50%)	20 (50%)



Fifty percent of the participants responded with the correct name, Vaniqa. The incorrect written and verbal responses are as follows in Table II

	<u>Incorrectly Interpreted</u>
Written Outpatient	Variqa
	Vancomycin*
	Varyc(2)
	Vanycin(2)
	Vanqc
	Vanquicin
	Van
	Vanque
	Vangia
	Varigo
Written Inpatient	Vaviga
	Varriga
Verbal	Zynoric
	<u>Phonetic Variable Responses</u>
	Soneca
	Seneca
	Phenica
	Vinica
Fanica	

* currently approved generic name product

C. SAFETY EVALUATOR RISK ASSESSMENT

Results of the verbal and written analysis show 20 participants interpreted the proprietary name, Vaniqa, correctly. Our studies did not substantiate the concern voiced by the expert panel that Viagra, might pose potential for medication errors due to sound-alike and look-alike similarity. However, we did uncover one overlapping existing approved drug product, vancomycin, in our outpatient prescription study. One participant interpreted Vaniqa as vancomycin. Vancomycin is

a generic name for Vancocin, an antibiotic mainly indicated for staphylococcal infection (including methicillin-resistant staphylococci). It is available as an injectable formulation and its usual adult dosage is 500 mg to 2 gm IV per day in 3 to 4 divided doses for 7 to 10 days. Vaniqa is available as a topical cream and is indicated for the treatment of excessive facial hair in women. There is no overlapping administration dosing schedule and strength between Vaniqa and vancomycin. Considering all the circumstances under which Vaniqa will be used, it is unlikely that vancomycin would be confused and result in potential medication errors.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Vaniqa, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. The sentence, "Apply to affected area twice daily", is listed twice on the side panel of the 30 and _____ labels. We would recommend this be stated in the "Usual Dosage" statement.
2. CFR 201.1 (h) (5) requires that if the distributor is named on the label, the name shall be qualified by various phrases.
3. See comment below concerning the _____ tube.

B. CARTON LABELING

See comments under CONTAINER LABEL

C. INSERT LABELING

The _____ tube is not listed under "How Supplied" section. We assume that this package size will not be marketed but will be used as a professional sample. If this is true, we recommend that the _____ label state "Professional Sample - Not for sale".

IV. RECOMMENDATIONS

1. OPDRA has no objections to the use of the proprietary name Vaniqa.
2. OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to meet with the Division for further discussion, if needed.

NDA- 21-145

Office Files

HFD-540; Millie Wright, Project Manager, DDDDP

HFD-540; Johnathan Wilkin, M.D., Division Director, DDDDP

HFD-042; Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)

HFD-430; Marilyn Pitts, Safety Evaluator, DDREI, OPDRA

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

JUL 26 2000

NDA/BLA Number: 21145 Trade Name: VANIQA(EFLORNITHINE HCL)15%TOPICAL CREAM

Supplement Number: Generic Name: EFLORNITHINE HCL

Supplement Type: Dosage Form: CRM

Regulatory Action: AP Proposed Indication: Indicated for the reduction of unwanted facial hair in women.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)

Infants (1-24 Months) Adolescents (12-16 Years)

Label Adequacy Adequate for SOME pediatric age groups *Can extrapolate safety and efficacy*

Formulation Status

Studies Needed

Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The use is Vaniqa in pediatric patients under the age of 12 is unlikely. See attached letter issue by Agency 5/16/00. M.Wright 7/26/00

Because the safety profile for an 18 year old and 12 year old would not be different for this drug & indication, the data submitted can support labeling down to age 12. M.Wright 7/25/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MILDRED WRIGHT

LSJ Signature 7/26/00 Date

Attachment (1) LSJ 7/26/00

ce
 C:\NOA 21145
 HFD-540/Div File
 HFD-540/Wright

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cc:

NDA 21-145
HFD 540 Division File
HFD 540/KozmaFornaro
HFD 540/Wright
HFD 540/Wilkin
HFD 540/Walker/5/11/00
HFD 540/Cook/5/11/00
HFD 104/D. Murphy
HFD 104/Roberts
HFD 104/T.Crescenzi
HFD 104/Locklear

Drafted: MJKF/5/15/00
Final: MJKF/5/15/00
Filename: 21145LSPEXC

LETTER SENT (LS)

LSJ

B1 5/15/00

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ON ORIGINAL



Doc. Rm.

Food and Drug Administration
Rockville MD 20857

MAY 19 2000

Amy McMichael, M.D.
Department of Dermatology
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, North Carolina 27157

Dear Dr. McMichael:

Between March 2 and 3, 2000, Ms. Eileen J. Bannerman, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #BMS-203522) of the investigational drug Vaniga (eflornithine hydrochloride topical cream), performed for Bristol-Myers Squibb. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Bannerman during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

KSJ

fi Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

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Food and Drug Administration
Rockville MD 20857

MAY 10 2000

Marty E. Sawaya, M.D.
230 S. W. Third Avenue
Ocala, Florida 34474

Dear Dr. Sawaya:

Between March 7 and 13, 2000, Ms. Brunilda Torres, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #BMS-203522) of the investigational drug Vaniga (eflornithine hydrochloride topical cream), performed for Bristol-Myers Squibb. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects

We appreciate the cooperation shown Investigator Torres during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

151

for! Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855



DEPARTMENT OF HEALTH & HUMAN SERVICES

Wright
Dec. Rom

Food and Drug Administration
Rockville MD 20857

Geoffrey P. Redmond, M.D.
Center for Health Studies, Inc.
23250 Chagrin Boulevard, Building 5
Suite 325
Beachwood, Ohio 44122

APR 28 2000

Dear Dr. Redmond:

Between March 1 and 3, 2000, Ms. Lori A. Lahmann, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #BMS-203522) of the investigational drug Vaniga (eflornithine hydrochloride topical cream), performed for Bristol-Myers Squibb. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that except for not reporting two adverse events for subject #849 to the sponsor, you adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We acknowledge your response and your promise to make corrections/changes in your procedures to ensure that the finding noted above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Lahmann during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

LSI

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

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Executive CAC
May 2, 2000

MAY 3 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Al DeFalice, Ph.D., HFD-110, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Team Leader
Barbara Hill, Ph.D., HFD-540, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-145

Drug Name: Vaniga (eflornithine HCl 15% cream; BMS-203522; DFMO)

Sponsor: Westwood-Squibb Colton Holdings Partnership

Background:

Eflornithine HCl is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis of ornithine to putrescine. Putrescine and other polyamines (i.e., spermidine and spermine) are present in all living cells and are considered to play an important role in the regulation of cell growth and differentiation. ODC is present in the hair follicle and would be required for hair growth in this tissue. Eflornithine HCl is an inhibitor of ODC and is being developed as a topical product to reduce the rate of growth of unwanted facial hair in hirsute women.

Mouse Carcinogenicity Study:

The following dose groups were tested in the study: untreated control, vehicle control, 150 mg/kg (25 μ l of 15% BMS-203522 cream), 300 mg/kg (50 μ l of 15% BMS-203522 cream) and 600 mg/kg (100 μ l of 15% BMS-203522 cream). The highest dose for this dermal carcinogenicity study was based on the maximum feasible concentration (15%) of BMS-203522 in the vehicle and the maximum feasible volume (100 μ l) that can be applied to the mouse. The protocol for this dermal carcinogenicity study was presented to the Executive CAC on 2/21/95. Concurrence for the dose selection and protocol were obtained on 3/7/95.

No biologically or statistically significant increase in tumors was noted for treated animals vs vehicle treated or untreated control animals. No evidence of carcinogenicity was noted for 15% BMS-203522 cream under the conditions of this mouse dermal carcinogenicity study. Therefore, 15% BMS-203522 cream was negative in the 2 year mouse dermal carcinogenicity study under the conditions used in the study.

**APPEARS THIS WAY
ON ORIGINAL**

Executive CAC Recommendations and Conclusions:

1. The committee determined that the mouse dermal carcinogenicity study was adequate and concurred that the study results were negative for carcinogenicity.
2. The committee recommended asking the sponsor for the starting and ending date for the study (a GLP question):
3. The committee recommended that human AUC values be obtained to calculate fold exposure levels for the mouse dermal carcinogenicity study.

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05/03/00

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:

NOA2145
/Division File, HFD 540
/Abby Jacobs, HFD-540
/Barbara Hill, HFD-540
/Millie Wright, HFD-540
/ASeifried, HFD-024

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