# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 21-145

## CORRESPONDENCE

Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000

HES4

NEW CORR

Worldwide Regulatory Affairs

# General Correspondence
## (Four Month Safety Update)

**NDA 21-145**
**Vaniqa™ (eflornithine HCl, 15% cream)**

January 24, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850


Dear Dr. Wilkin,

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine HCl, 15% cream) and to the requirement noted in 21 CFR 314.50(d)(5)(vi)(b) for a 4 month safety update following the initial submission of an NDA.

In response to that requirement, we note that there are no clinical or preclinical studies in progress with respect to the filed indication. Therefore the Integrated Summary of Safety provided in the original submission of this NDA is unchanged, and no changes are proposed in the draft labeling submitted for this product.. Studies in ——— indication of ——————— are ongoing under IND ——— and progress in these studies was summarized in the most recent annual report to that IND

If you should require any further information regarding this application, please contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

DUPLICATE

Kathy B. Schrode, Ph.D.
Group Director, Life Style Enhancement
Regulatory Sciences

KBS/pc

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)*

*Expiration Date: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Bristol-Myers Squibb Company | January 24, 2000 |
| TELEPHONE NO. *(Include Area Code)* 609-252-4000 | FACSIMILE (FAX) Number *(Include Area Code)* 609-252-6000 |
| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: P.O. Box 4000 Princeton, NJ 08543-4000 | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-145

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Eflornithine hydrochloride | VANIQA |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)* |
|---|---|
| difluoromethyl-D,L-ornithine monohydrochloride | BMS-203522 |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Cream | 15% | Topical |

(PROPOSED) INDICATION(S) FOR USE:
Treatment of excessive facial hair in women

## APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, [illegible] 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 SUBMISSIO
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RE[illegible]ION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ [illegible]
☐ 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 _____ THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, [illegible]ing and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, re[illegible] 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.

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

| | |
|---|---|
| | 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)) |
| | 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 314.50 (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 |
|---|---|---|
| David L. Schrode for KBS | Kathy B. Schrode, Ph.D., Director, Regulatory Sciences | January 24, 2000 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| P.O. Box 4000, Princeton, NJ 08543-4000 | ( 609 ) 252-6463 |

**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.

Please **DO NOT RETURN** this form to this address.

# Bristol-Myers Squibb
## Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

July 27, 2000

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Subject:** **NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**
**Phase IV Commitment**

Dear Dr. Wilkin:

Reference is made to the teleconference between Dr. Wilkin, Ms. M. Wright, Dr. S. Hathaway and Mr. E. Papas of the FDA and Dr. K. Schrode, Mr. W. Regan and Mr. N. Mavinkurve of Bristol-Myers Squibb Company on July 27, 2000. Reference is also made to the Amendment to the subject Application dated July 26, 2000, which included a commitment to provide data on ——— and to ——— In accordance with the discussion of July 27, 2000, Bristol-Myers Squibb Company withdraws the commitment in the Amendment of July 26 and agrees to the Phase IV commitment included in this Amendment.

Bristol-Myers Squibb Company certifies that in accordance with 21 CFR 314.70(a), a true copy of this Amendment is being provided to the North Brunswick office of the Food and Drug Administration.

If you have any questions, please do not hesitate to contact me at (609) 818-4732 or Nandan Mavinkurve at (609) 818-5386.

Sincerely,

W. J. Regan

William J. Regan
Director
CMC for Marketed Products, North America
Worldwide Regulatory Affairs

Enclosures

fax

# Bristol-Myers Squibb
## Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

**Kathy B. Schrode, Ph.D.**
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

**RESPONSE TO FDA DRAFT LABELING**

July 27, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15% and to the teleconference between the FDA and BMS held on July 27, 2000 to discuss labeling of this product.

Attached is the package insert and patient information leaflet incorporating all the changes agreed to at this meeting.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk Copy: Ms. Millie Wright (HFD-540)

A Bristol-Myers Squibb Company

Post-it™ brand fax transmittal memo 7671 | # of pages ▸ 14

| | |
|---|---|
| To M. Wright | From R. Biamini |
| Co. FDA | Co. BMS |
| Dept. | Phone # (609-252-5357 |
| Fax 301-827-2091 | Fax # |

609 252 6000

fax

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

**RESPONSE TO FDA DRAFT LABELING**

July 27, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15%.

Attached is the revised package insert and patient information leaflet incorporating the following changes:

- An * is added to the figures with a definition.
- The ———— is deleted from the "How should Vaniqa be stored" section of the patient information leaflet. A period is added after the ( ).
- The spelling of Clinical in the overdosage section was corrected.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk Copy: Ms. Millie Wright (HFD-540)

A Bristol-My

Post-it™ brand fax transmittal memo 7671 | # of pages ▸ 14

| | |
|---|---|
| To M. Wright | From K. Bi... |
| Co. FDA | Co. BMS |
| Dept. | Phone # 609-252-5357 |
| Fax # 301-827-2091 | Fax # |

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

**RESPONSE TO FDA DRAFT LABELING**

July 26, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15% and to a telephone conversation between M. Wright (FDA) and K. Schrode (BMS) held on July 26, 2000 to discuss labeling of this product.

Attached is the package insert and patient information leaflet incorporating all the changes agreed to during this phone call.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk Copy: Ms. Millie Wright (HFD-540)

fax

**Bristol-Myers Squibb**
**Pharmaceutical Research Institute**
P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

July 26, 2000

Jonathan K. Wilkins, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Subject:** **NDA 21-145**
**Eflornithine Hydrochloride Cream, 15%**
**Phase IV Commitment**

Dear Dr. Wilkins:

This Amendment is submitted in response to a request from Ms. M. Wright for a commitment to provide data on the ——— of the product in response to Comment No. 8(a) of FDA letter dated June 23, 2000.

Reference is made to FDA letter dated June 23, 2000 and specifically to Comment No. 8(a) which requested a commitment to perform studies to determine the cause of the and whether the ——————————. Reference is also made to the teleconference between Ms. M. Wright, Dr. W. DeCamp and Mr. E. Papas of the FDA and Dr. K. Schrode and Mr. N. Mavinkurve of Bristol-Myers Squibb Company on June 28, 2000 as well as the Amendment to the subject Application dated July 7, 2000 wherein the response to Comment No. 8(a) was discussed. Further, in accordance with the discussion of July 26, 2000 between Ms. M. Wright, Mr. E. Papas, Dr. K. Schrode and Mr. W. Regan, a commitment to provide data on ——— and to evaluate ——————————; is included in this Phase IV Commitment. Also as discussed in the last teleconference, it was agreed that the BMS response to Comment No 8(b) is complete and satisfactory and no further information is required by the FDA.

Bristol-Myers Squibb Company certifies that in accordance with 21 CFR 314.70(a), a true copy of this Amendment is being provided to the North Brunswick office of the Food and Drug Administration.

If you have any questions, please do not hesitate to contact me at (609) 818-4732 or Nandan Mavinkurve at (609) 818-5386.

Sincerely,

N Mavinkurve

for William J. Regan
Director
CMC for Marketed Products, North America
Worldwide Regulatory Affairs

**Phase IV Commitment to Provide ——— Data And Evaluate ———**

Bristol-Myers Squibb Company agrees to a Phase IV commitment to add a test and provide data on ——— of the product on the first three commercial production batches placed on stability storage as a part of our marketlife stability program. Available data on the test for ——— of the product will be reported in Annual Reports.

Furthermore, Bristol-Myers Squibb agrees to a Phase IV commitment to evaluate potential ——— and continue a dialog with the Agency on this matter. Bristol-Myers Squibb expects to complete this activity within one year.

(76)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08543-5400 609 818-3000

July 24, 2000

NDA DRUG AMENDMENT


Jonathan K. Wilkins, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Subject:** **NDA 21-145**
**Eflornithine Hydrochloride Cream, 13.9%**
**Amendment to a Pending Application**

BC

Dear Dr. Wilkins:

Reference is made to the teleconference between FDA and the Bristol-Myers Squibb Company on July 24, 2000. In the teleconference, FDA requested Bristol-Myers Squibb Company to submit an Amendment containing a request for categorical exclusion from submitting an environmental assessment as required by 21CFR§25.31(b). Accordingly, an Environmental Statement containing the categorical exclusion is included in this Amendment.

Bristol-Myers Squibb Company certifies that in accordance with 21 CFR 314.70(a), a true copy of this Amendment is being provided to the North Brunswick office of the Food and Drug Administration.

We trust the information included in this Amendment is complete and satisfactory. If you have any questions, please do not hesitate to contact me at (609) 818-4732 or Nandan Mavinkurve at (609) 818-5386.

Sincerely,

Mavinkurve

For William J. Regan
Director
CMC for Marketed Products, North America
Worldwide Regulatory Affairs

Enclosures

Cc: Food and Drug Administration
North Brunswick Office
120 North Center Drive
North Brunswick, NJ 08902

ORIGINAL

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science



## NDA ORIG AMENDMENT

**RESPONSE TO FDA DRAFT LABELING**

July 24, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

BL

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15% and to the teleconference between the FDA and BMS held on July 24, 2000 to discuss labeling of this product.

Attached is the package insert and patient information leaflet incorporating all the changes agreed to at this meeting.

At the next printing, we agree to update the packaging components to reflect the updated wording in the package insert regarding the "contains" statement and the listing of the inactive ingredients in alphabetical order.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk Copy: Ms. Millie Wright (HFD-540)

DUPLICATE

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

AMENDMENT
BL

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science



**RESPONSE TO FDA DRAFT LABELING**

July 21, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15% and our submission dated July 20, 2000 providing a response to FDA draft labeling.

As requested, we are providing an electronic copy [ tube30.pdf, carton30.pdf, and carton60.pdf]. The requested electronic files are being provided on one diskette. The total size of the files are less than 1.4 MB. The file was screened for known viruses on July 21, 2000, with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected. An additional copy of the diskette is provided to Millie Wright as a desk copy.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk copy: Ms. Millie Wright (HFD-540)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

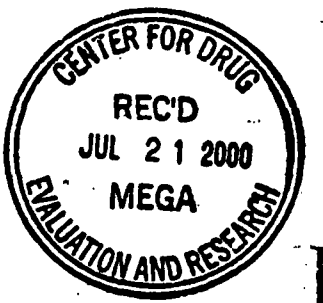
P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

**Kathy B. Schrode, Ph.D.**
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science


AMENDMENT
BL

## RESPONSE TO FDA DRAFT LABELING

July 20, 2000




**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for VANIQA (eflornithine hydrochloride) Cream, 15% and to the draft package insert received from the FDA on July 18, 2000.

Enclosed are:

- Revised tube (30g) and carton (30g and 60g) graphics incorporating the following changes:
  - Change of strength, spelling out of hydrochloride
  - Placing the "Cream" outside the parenthesis
  - Change of case for the generic name to parallel the draft package insert
  - Incorporation of text describing the anhydrous and monohydrate concentration
  - Deletion of [redacted] to parallel the draft package insert
  - Deletion of [redacted]
- Proposed draft labeling in two formats:
  - Three columns, side by side with FDA draft, BMS proposed changes only, rationale for the changes. Please note that the AR table and the figures are provided separately.
  - A complete draft incorporating BMS proposed changes.

In addition to the hard copy report, a diskette is included containing the proposed draft labeling. The electronic portion of the submission consists of two files (proposed.doc and changes.doc) on one 3.5 inch diskette which is enclosed in the Archival copy. The total size of the files are less than 1.4 MB. The file was screened for known viruses on July 20, 2000, with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected. An additional copy of the diskette is provided to Millie Wright as a desk copy.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director
Life Style Enhancement
Regulatory Sciences

KBS/kb
Attachments
Desk copy: Ms. Millie Wright (HFD-540) – Hard copy and disk. PDF file of tube and cartons in electronic format to follow under separate cover.

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liason and Global Strategy Unit
Regulatory Science



AMENDMENT
BS

**RESPONSE TO FDA REQUEST FOR INFORMATION**

**NDA 21-145**
**Vaniqa® (eflornithine HCl cream) 15%**

July 17, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin,

Reference is made to NDA 21-145 for Vaniqa® (eflornithine HCl cream) 15% for excessive unwanted facial hair in women and to a teleconference between the FDA and BMS on Wednesday July 12, 2000.

Attached, as requested, are the additional statistical analyses on the Subject self assessment. In addition to the hard copy report, a diskette is included containing the SAS programs and datasets. The electronic portion of the submission consists of 22 files in two folders on one 3.5 inch diskette which is enclosed in the Archival copy. The total size of the electronic submission is approximately 1.36 MB. The file was screened for known viruses on July 14, 2000, with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected. An additional copy of the diskette is provided to Millie Wright as a desk copy.

The data are very positive for each of the six questions in the Subject self assessment in each study. It is interesting to note that the question with the greatest change from baseline, active versus vehicle, was: How much were you bothered by the

time spent removing hair? This observation is consistent with the pharmacology of the product, reduction in the rate of hair growth.

If you have any additional questions, please do not hesitate to contact me by phone at 609-252-6463 or by FAX at 609-252-6000.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director,
Life Style Enhancement
Regulatory Sciences

KBS/CM/lp
Attachments

CC: Millie Wright, Project Manager [by fax]

APPEARS THIS WAY
ON ORIGINAL

(74)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000



**Kathy B. Schrode, Ph.D.**
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

**GENERAL CORRESPONDENCE**

July 11, 2000

NEW CORRESP
NC

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine hydrochloride cream) 15%, to an e-mail from Dr. W. DeCamp dated July 3, 2000, and to a teleconference between the FDA and BMS on July 5, 2000. These recent discussions covered the issue of the calculation of strength.

The nomenclature of the drug substance as given in the USAN in eflornithine hydrochloride, which is defined as eflornithine hydrochloride monohydrate. Therefore, after careful consideration, we believe that based on the USAN definition, we have appropriately represented the concentration as 15%. Attached for ease of reference is the USAN listing for eflornithine hydrochloride. This representation is also consistent with nomenclature and labeling for the injectable form of this drug substance. We can clarify this concept further by adding this statement to the package insert as follows:

Statement in the **DESCRIPTION** section of the package insert as currently submitted to the FDA:

[ ]

Proposed modification of the statement:

[redacted]

We are available for further discussion on this matter if need be. Please contact me via FAX at (609) 252-6000 or by telephone at (609) 252-6463.

Sincerely,

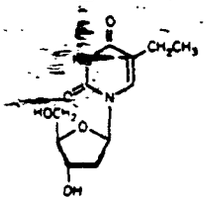
Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
FDA Liaison and Global Strategy Unit

KBS/kb
Attachment
cc: Millie Wright via FAX (301) 827-2075
Ernest Pappas via FAX (301) 827-2075

[redacted]

APPEARS THIS WAY
ON ORIGINAL

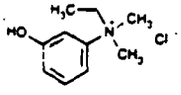
**Edoxudine** [*1984*] (e dox' yoo deen). $C_{11}H_{16}N_2O_5$. 256.26. (1) Uridine, 2'-deoxy-5-ethyl-; (2) 2'-Deoxy-5-ethyluridine. *CAS-15176-29-1*. INN. *Antiviral*. (Ortho Pharmaceutical, Canada) ✧*EDU; EUDR; ORF 15817; RWJ 15817*



**Edrecolomab** [*1996*] (ed re kol' oh mab). (1) Immunoglobulin G 2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer; (2) Immunoglobulin G 2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer. Molecular weight is approximately 148,000 daltons. *CAS-156586-89-9*. INN. *Monoclonal antibody* (*antineoplastic adjuvant*). Panorex (Centocor) ✧*C-1*

Edrophone Chloride — *See* Edrophonium Chloride.

**Edrophonium Chloride** (ed roe foe' nee um). USP. $C_{10}H_{16}ClNO$. 201.70. (1) Benzenaminium, *N*-ethyl-3-hydroxy-*N*,*N*-dimethyl-, chloride; (2) Ethyl(*m*-hydroxyphenyl)dimethylammonium chloride. *CAS-116-38-1; CAS-312-48-1* [edrophonium]. INN; BAN; JAN. *Antidote* (*to curare principles*); *diagnostic aid* (*myasthenia gravis*). Enlon (Anaquest); Reversol (Organon); Tensilon (ICN); component of Enlon Plus (Anaquest)



EDTA — *See* Edetic Acid.

EDTA Calcium — *See* Edetate Calcium Disodium.

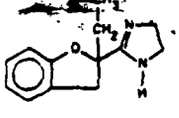
EDU. Code designation for Edoxudine.

E.E.ME. Code designation for Mestranol.

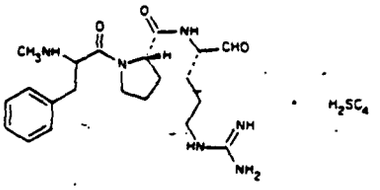
E.E.S. Abbott brand of Erythromycin Ethylsuccinate.

EF9. Code designation for Temoporfin.

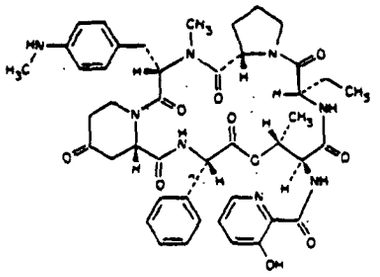
Efaroxan. $C_{13}H_{16}N_2O$. 216.[illegible] (±)-2-(2-Ethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoli[illegible] *CAS-89197-32-0*. INN; BAN.



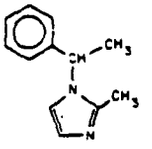
**Efegatran Sulfate** [*1994*] (ef' e ga tran). $C_{21}H_{32}N_6O_3.H_2SO_4$. 514.61. [Efegatran is INN.] (1) L-Prolinamide, *N*-methyl-D-phenylalanyl-*N*-[4-[(aminoiminomethyl)amino]-1-formylbutyl]-, (*S*)-, sulfate (1:1); (2) *N*-Methyl-D-phenylalanyl-*N*-[(1*S*)-1-formyl-4-guanidinobutyl]-L-prolinamide sulfate (1:1). *CAS-126721-07-1; CAS-105806-65-3* [efegatran]. *Antithrombotic*. (Lilly) ✧*LY294468 sulfate*



Efepristin. $C_{44}H_{52}N_8O_{10}$. 852.95. *N*-[(6*R*,9*S*,10*R*,13*S*,15a*S*,22*S*,24a*S*)-6-Ethyldocosahydro-10,23-dimethyl-22-[*p*-(methylamino)benzyl]-5,8,12,15,17,21,24-heptaoxo-13-phenyl-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide. *CAS-57206-54-9*. INN.

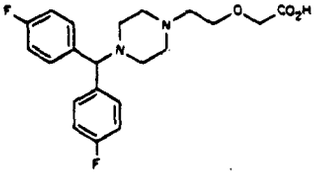


Efetozole. $C_{12}H_{14}N_2$. 186.26. (±)-2-Methyl-1-(α-methylbenzyl)imidazole. *CAS-99500-54-6*. INN.

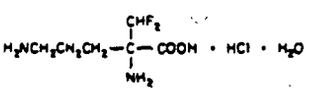


Effexor. Wyeth-Ayerst brand of Venlafaxine Hydrochloride.

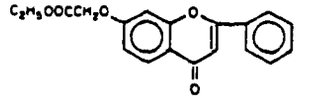
Efletirizine. $C_{21}H_{24}F_2N_2O_3$. 390.43. [2-[4-[Bis(*p*-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid. *CAS-150756-35-7*. INN.



**Eflornithine Hydrochloride** [*1986*] (ee flor' ni theen). $C_6H_{12}F_2N_2O_2.HCl.H_2O$. 236.65. [Eflornithine is INN and BAN.] (1) DL-Ornithine, 2-(difluoromethyl)-, monohydrochloride, monohydrate; (2) 2-(Difluoromethyl)-DL-ornithine monohydrochloride, monohydrate. *CAS-96020-91-6; CAS-67037-37-0* [eflornithine]. *Antineoplastic; antiprotozoal*. Ornidyl (Merrell) ✧*MDL 71,782 A*



Efloxate. $C_{19}H_{16}O_5$. 324.34. Ethyl-[(4-oxo-2-phenyl-4*H*-1-benzopyran-7-yl)oxy] acetate. *CAS-119-41-5*. INN; JAN; MI.



* Brand name formerly used, and/or firm no longer concerned with this product.

(15)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000 609 921-4000


July 11, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan K. Wilkin, M.D. Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

AMENDMENT
BC

Dear Dr. Wilkin:

This Amendment is submitted to withdraw the Bristol-Myers Squibb facility at Humacao, PR as an additional site of manufacture.

Reference is made to the teleconference on April 4, 2000 between Ms. Millie Wright, Dr. Wilson DeCamp, and Mr. Ernest Pappas of the FDA and Dr. Kathy Schrode, Mr. William Regan, and Mr. Nandan Mavinkurve of the Bristol-Myers Squibb Company in which the inclusion of the Humacao site was discussed. Accordingly, we had provided for the Humacao site as an additional site of manufacturing, packaging and testing of the drug product in the Amendment dated May 4, 2000 with the understanding that if the FDA inspection of the facility could not be scheduled in a timely manner, we would be withdrawing the Humacao facility. As discussed in the teleconference on June 28, 2000 between Ms. Millie Wright, Dr. Wilson DeCamp, Mr. Ernest Pappas, Dr. Kathy Schrode and Mr. Nandan Mavinkurve, we are withdrawing the Humacao site at this time to maintain the timeline for a July action letter without prejudice to providing for this site after the approval of the NDA. It was agreed that the existing stability package would be acceptable for the future sNDA.

Bristol-Myers Squibb Company certifies that in accordance with 21CFR§314.70(a), a true copy of this Amendment is being provided to the North Brunswick Office of the Food and Drug Administration.

We trust this is satisfactory. If you have any questions, please do not hesitate to contact me by telephone at (609) 818-4732.

Sincerely,

William J. Regan
Director
CMC-Marketed Products, North America

Cc: Food and Drug Administration
North Brunswick Office
120 North Center Drive
North Brunswich, NJ 08902

Desk copy: Ernest Pappas via FAX (301) 827-2075
Millie Wright via FAX (301) 827-2075

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA [illegible] AMENDMENT



**RESPONSE TO FDA REQUEST FOR INFORMATION**

BM

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

July 11, 2000

Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine hydrochloride cream) 15% and to the request for information on leukopenia and elevated liver function tests faxed on May 30, 2000.

Attached are the responses:

- A very thorough review of the liver function results from all subjects in all studies is presented. Any subject who had an out of range value is presented in the listings with values that were $\geq$ 1.5 or $\geq$ times the upper limit of normal flagged (* and **, respectively).

- Tables for all subjects in all studies who had shifts from baseline in WBC and neutrophils were generated. All subjects who had an adverse event of leukopenia (neutropenia was coded as leukopenia) were examined in greater detail by looking at the WBC and differential.



ORIGINAL

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Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategic
Regulatory Science



NDA [illegible]ENT

**RESPONSE TO FDA REQUEST FOR INFORMATION**

May 24, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine HCl 15% cream)**

DB

Mary Jean Kozma Fornaro,
Supervisor, Project Management Staff
Center for Drug Evaluation and Research
Div. of Dermatologic and Dental
Drug Products. HFD-540
9201 Corporate Blvd.
Building 2, 2nd Floor
Rockville, MD. 20850

Dear Ms. Fornaro:

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine HCl 15% cream).

In response to your telephone request of May 22, 2000, we are enclosing copies of the following study reports, corresponding to references 14 through 18 in the Human Pharmacokinetics and Bioavailability Summary, Vol. 1.32, for use by FDA's Biopharm reviewers.

- Franz TJ. Evaluation of the bioavailability of three formulations of eflornithine hydrochloride lotion by *in vitro* cadaver skin permeation. Bristol-Myers Squibb Pharmaceutical Research Institute 1996: Report no. 910000208.

- Chou J and Parab P. Summary of the *in vitro* skin permeation profile of BMS-203522-01 (eflornithine) from different topical formulations during product development. Bristol-Myers Squibb Pharmaceutical Research Institute 1999; Report no. 920000051.

- Ahuwalia GS. Metabolism of topically applied DFMO in adult women (study no. GMEH 2971). Gillette Research Institute Report 1991.



ORIGINAL

- Ahuwalia GS. Absorption/excretion of topically applied DFMO in adult women (study no. GMEH 2971). Gillette Research Institute Report 1991.

- Malhotra BK. Percutaneous absorption and pharmacokinetics of BMS-203522 in hirsute women after a single application and after one week of twice-daily application of a 15% w/w cream formulation of BMS-203522. Bristol-Myers Squibb Pharmaceutical Research Institute 1999; Report no. 910074577.

If I can be of any further assistance in connection with this application, please feel free to contact me by telephone at (609) 252-6463, by FAX at (609) 252-6000.

Sincerely yours,

Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
FDA Liaison and Global Strategy Unit

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 page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## CANT INFORMATION

| | |
|---|---|
| OF APPLICANT: Westwood-Squibb Colton Holdings Partnership | DATE OF SUBMISSION: July 11, 2000 |
| ONE NO. *(Include Area Code)*: 609-252-4000 | FACSIMILE (FAX) Number *(Include Area Code)*: 609-252-6000 |
| CANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, S License number if previously issued)*:<br>Scudders Mill Road<br>ceton, NJ 08536 | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 12 2000
MEGA

## DUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): NDA 21-145

| | |
|---|---|
| BLISHED NAME *(e.g., Proper name, USP/USAN name)*: rnithine hydrochloride | PROPRIETARY NAME *(trade name)* IF ANY: VANIQA |
| ICAL,BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: oromethyl-D,L-ornithine monohydrochloride | CODE NAME *(If any)*: BMS-203522 |
| AGE FORM: m | STRENGTHS: 15% |
| ROUTE OF ADMINISTRATION: Topical | |

POSED) INDICATION(S) FOR USE:
tment of excessive facial hair in women

## LICATION INFORMATION

LICATION TYPE (ck one)
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

N NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

N ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
e of Drug — Holder of Approved Application

E OF SUBMISSION (ck 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

ASON FOR SUBMISSION
sponse to FDA Request for Information

POSED MARKETING STATUS (check o ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

MBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## STABLISHMENT INFORMATION

vice locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, dress, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) ducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

| | |
|---|---|
| [redacted] 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 Microbioblogy (e.g. 21 CFR 314.50 (d) (4)) | |
| 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 314.50 (k) (3)) | |
| 18. User Fee Cover Sheet (Form FDA 3397) | |
| 19. OTHER (Specify) Response to FDA Request for Information | |

TIFICATION

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

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

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

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

ning: 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 |
|---|---|---|
| [signature] | Kathy B. Schrode, Ph.D., Group Director, Life Style Products | July 11, 2000 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| P.O. Box 4000, Princeton, NJ 08[redacted] | ( 609 ) 252-6463 |

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

HS, Reports Clearance Officer
perwork Reduction Project (0910-0338)
bert H. Humphrey Building, Room 531-H
0 Independence Avenue, S.W.
ashington, DC 20201

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ease DO NOT RETURN this form to this address.



M FDA 356h (7/97)

(61)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08540 609 818-5000



July 6, 2000

NDA ORIG AMENDMENT

Jonathan K. Wilkins, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Subject:** **NDA 21-145**
**Eflornithine Hydrochloride 15% Cream**
**Information Request**

B.C

Dear Dr. Wilkins:

Reference is made to our pending NDA 21-145 submitted on September 27, 1999. Further reference is made to the information request dated June 23, 2000, and the teleconference between BMS (K. Schrode. N. Mavinkurve) and FDA (M. Wright, T. DeCamp. E. Papas) on June 28. 2000 to discuss proposed answers to these questions. As requested. we are now providing responses to each of the questions.

Bristol-Myers Squibb Company certifies that in accordance with 21 CFR 314.70(a), a true copy of this Amendment is being provided to the New Jersey District Office of the Food and Drug Administration.

We trust the information included in this Amendment is complete and satisfactory. If you have any questions. please do not hesitate to contact me at (609) 818-4732 or Nandan Mavinkurve at (609) 818-5386.

Sincerely.

Bristol-Myers Squibb Company

ORIGINAL

William J. Regan
Director
CMC-Marketed Products North America

Enclosures

cc: Food and Drug Administration
North Brunswick Office
129 North Center Drive
North Brunswick, NJ 08902

Desk copy: Mr. Ernest Pappas
Division of Dermatologic and Dental Products (HFD-540)

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 page 2.*

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| PHONE NO. *(Include Area Code)*: 609-252-4000 | FACSIMILE (FAX) Number *(Include Area Code)*: 609-252-6000 |
| ICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code. U.S. License number if previously issued)*: 7 Scudders Mill Road, nceton, NJ 08536 | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

CENTER FOR DRUG EVALUATION AND RESEARCH RECD JUL 10 MEGA

## DUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-145

| | |
|---|---|
| BLISHED NAME *(e.g., Proper name, USP/USAN name)*: nithine hydrochloride | PROPRIETARY NAME *(trade name)* IF ANY: VANIQA |
| ICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: oromethyl-D,L-ornithine monohydrochloride | CODE NAME *(If any)*: BMS-203522 |
| AGE FORM: um | STRENGTHS: 15% |
| ROUTE OF ADMINISTRATION: Topical | |

POSED) INDICATION(S) FOR USE:
tment of excessive facial hair in women

## LICATION INFORMATION

ICATION TYPE (k one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
of Drug — Holder of Approved Application

E OF SUBMISSION (k 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

ON FOR SUBMISSION
onse to Information Request Dated June 23, 2000

POSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

BER OF VOLUMES SUBMITTED [redacted] THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ABLISHMENT INFORMATION

de locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, ss, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) cted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

| pplication 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)) | | |
| 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 314.50 (k) (3)) | | |
| 18. User Fee Cover Sheet (Form FDA 3397) | | |
| 19. OTHER (Specify) Response to Information Request Dated June 23, 2000. | | |

FICATION

to update this application with new safety information about the product that may reasonably affect the statement of contraindications, gs, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as ted by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, ng, but not limited to the following:
Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
Biological establishment standards in 21 CFR Part 600.
Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
Local, state and Federal environmental impact laws.
application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the t until the Drug Enforcement Administration makes a final scheduling decision.
ata and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
ng: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| TURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| | William J. Regan, Director CMC Marketed Products | July 6, 2000 |
| ESS *(Street, City, State, and ZIP Code)* | Telephone Number | |
| Box 4000, Princeton, NJ [redacted] | ( 609 ) 818-4732 | |

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

S. Reports Clearance Officer
rwork Reduction Project (0910-0338)
rt H. Humphrey Building, Room 531-H
Independence Avenue, S.W.
hington, 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.

se DO NOT RETURN this form to this address.



FDA 356h (7/97)

(57)


# WESTWOOD-SQUIBB COLTON HOLDINGS PARTNERSHIP

777 Scudders Mill Road
Princeton, New Jersey 08536



**AMENDMENT TO A PENDING NDA:**
REVISED DRAFT LABELING

**NDA 21-145**
**VANIQA (eflornithine hydrochloride cream), 15%**

June 5, 2000

BL

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

This amendment to the above-referenced NDA for Vaniqa™ (eflornithine HCl cream), 15%, contains the following revised information with regard to the proposed draft labeling most recently submitted on March 2, 2000.

Electronic and hard copy mockups of the revised decoration (color scheme) for the cartons to be used for the 30 g and 60 g sizes proposed for marketing are provided. The text and its location on the carton remain unchanged from the previous amendment. Note that the 60 g carton will — contain two (2) 30 g tubes, ——— The package insert will also be modified to reflect this change in the **How Supplied** section. Tube graphics are not being changed.

Note that the originally submitted —— is **not** being withdrawn. At such time as marketing of the ——— is initiated, identification of the ——— as an available size will be restored to the package insert, and revised labeling provided to the N[redacted]in an annual report. The tube graphics and color scheme for the [redacted]arton will reflect the approved labeling then in effect.

A subsequent amendment is in preparation which will provide specifications and draft labeling for an alternate sample tube, utilizing the same cap and body resins as the trade and sample size tubes submitted in the original application.

We note, however, that if review of this amendment will have an adverse impact on the timing of an action with regard to the remainder of the application, Bristol-Myers Squibb

will withdraw the amendment. There are no other changes to the conditions and information submitted in the original New Drug Application.

The electronic documents provided in this submission have been prepared and organized in conformance with the 1999 Guidance for Industry: Providing Regulatory Submissions in Electronic Format. The cover letter, Form 356h and table of contents are provided in both paper and electronic format. The electronic portion of the submission consists of two 3.5" disks containing 10 files and 2 folders. These files include the originally submitted insert (current.pdf), the proposed insert, in both Word97 (".doc") and Adobe Acrobat (".pdf") formats, and carton labeling, incorporating the requested changes. The total size of the electronic submission is less than 1.6 Mb. The files were screened for known viruses on June 5, 2000, with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected.

For the convenience of reviewers, those documents in the submission that are reproduced in electronic form contain hypertext links to other documents referenced within the text and tables. These hyperlinks for file names appear in blue type in the electronic document. Document names used in these tables generally conform to the scheme outlined in the FDA guidance. Also, invisible links, indicated by the cursor changing to a pointing finger, have been inserted from specific sections of carton text to the corresponding section of the proposed package insert (proposed.pdf).

Please note that the electronic table outlining the labeling history, labeling/history.pdf, includes a hyperlink to each of the proposed cartons and the package insert. No new clinical data are cited. The changes to the insert merely identify the alternate proposed market package. The file labeling/current.pdf includes the package insert which was provided in the original submission of this NDA. As the labeling is not yet approved, we have not included a file for an approved package insert.

We trust the information included in this Amendment is complete and satisfactory. If you have any questions, please do not hesitate to contact me at (609) 252-6463 or Nandan Mavinkurve at (609) 818-5386.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director, Lifestyle Products
Bristol-Myers Squibb Company

Enclosures
Desk copy: Mr. Ernest Pappas, Division of Dermatologic and Dental Drug Products (HFD 540)

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science



# NDA ORIG AMENDMENT

## RESPONSE TO FDA REQUEST FOR INFORMATION

May 19, 2000

**NDA 21-145**
**Vaniqa™ (eflornithine HC1 15% cream)**

BB

MaryJean Kozmo Fornaro,
Supervisor, Project Management Staff
Center for Drug Evaluation and Research
Div. of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd.
Building 2, 2nd Floor
Rockville, MD. 20850

Dear Ms. Fornaro:

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine HCl 15% cream).

In response to your original telephone request of April 25, 2000, we provided, on April 27, the contents of Section 6 [Human Pharmacokinetics] on CD-ROM in Adobe PDF format.

In response to FDA's subsequent request for this Human Pharmacokinetic section in a word processed, editable format, we are pleased to enclose a diskette containing the following files in MS Word format:

- **"PKSummaryNDAclin.doc"** – Corresponding to "Human Pharmacokinetics and Bioavailability Summary" Vol. 1.32: Section 6A [less Attachments, Bioanalytical Methods, and Literature References that carry over to Vol. 1.33, pages 1 to 164]. *Please note that line spacing on this report was subsequently reformatted so that it will no longer match page numbers in the submitted NDA.*

- **"de140003FSR.doc"** – Corresponding to Study No. DE140-003, "Percutaneous Absorption and Pharmacokinetics of BMS-203522 in Hirsute Women after a Single Application and after One Week of Twice-Daily Application of a 15% w/w Cream

Formulation of BMS-203522," 3/21/99 Vol. 1.34: Section 6.B.3 [less appendices that carry over to Vol. 1.35].

The remaining reports in Section 6 [Study No. GMEA 2971, "Metabolism of topically Applied DFMO in Adult Women," 10/17/91 and Study No. GMEA 2971, "Absorption / Excretion of Topically Applied $^{14}$C-DFMO in Adult Women," 12/6/91] were obtained from a contract laboratory and we have been unable to locate electronic versions of those reports.

If I can be of any further assistance in connection with this application, please feel free to contact me by telephone at (609) 252-6463, by FAX at (609) 252-6000.

Sincerely yours,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
FDA Liaison and Global Strategy Unit

APPEARS THIS WAY
ON ORIGINAL

39

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6465 Fax 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

## RESPONSE TO INFORMATION REQUEST

NEW CORRESP
AC 82

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

May 3, 2000

Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine hydrochloride 15% cream) and to the information requests made by FDA by telephone and FAX on March 21, 2000 and April 17, 2000, respectively.

We are pleased to provide responses to these requests as follows:

- In response to the telephone request of March 21, we are providing, in hard copy and on diskette, the SAS programs 6.12 used for the analyses in NDA 21-145

- In response to the FAX request of April 17, we are providing a summary of subject accounting information for DE140-001 and DE140-002 in FDA's requested tabular format.

If I can be of any further assistance in connection with this application, please feel free to contact me by FAX at (609) 252-6000 or by telephone at (609) 252-6463.

Sincerely,

Kathy B. Schrode

Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
FDA Liaison and Global Strategy Unit

Attachments
Desk Copy: Millie Wright, Project Manager

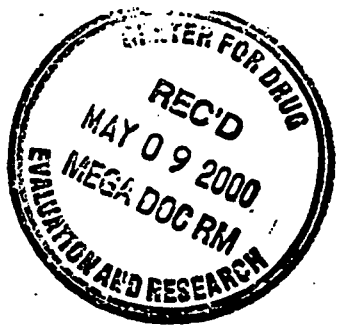
APPEARS THIS WAY
ON ORIGINAL

36

Bristol-Myers Squibb
Pharmaceutical Research Institute

NDA [illegible] AMENDMENT

May 1, 2000




Jonathan K. Wilkins, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**Subject:** **NDA 21-145**
**Eflornithine Hydrochloride 15% Cream**
**Amendment to a Pending Application**

BC

Dear Dr. Wilkins:

This Amendment contains information with regard to the following changes to the information submitted in our original New Drug Application on September 27, 1999:

1. Reference to the updated DMF submitted by [redacted] the [redacted] manufacturer
2. Bristol-Myers Squibb facility at Humacao, PR as an additional site of manufacturing, packaging and testing of the drug product
3. Change in the lower limit of the specifications for pH of the drug product
4. Change in the resin of the cap of the [redacted] sample tube
5. Change in the cartons for the 30 g tube and the [redacted]

These changes were discussed in a teleconference between Ms. Millie Wright, Dr. Anthony DeCamp and Mr. Ernest Pappas of the Division of Dermatologic and Dental Drug Products and Dr. Kathy Schrode, Mr. William Regan and Mr. Nandan Mavinkurve of the Bristol-Myers Squibb Company on April 4, 2000. As discussed in the teleconference, if the FDA pre-approval inspection of the Humacao site cannot be scheduled in a timely manner, or if compliance issues are found as a result of an FDA pre-approval inspection, Bristol-Myers Squibb will withdraw the Humacao site from the Application. Information pertaining to each of the above listed changes is included in relevant sections of this Amendment.

There are no other changes to the conditions and information submitted in the original New Drug Application.

Bristol-Myers Squibb Company certifies that in accordance with 21 CFR 314.70(a), a true copy of this Amendment is being provided to the New Jersey District Office of the Food and Drug Administration.

DUPLICATE

We trust the information included in this Amendment is complete and satisfactory. If you have any questions, please do not hesitate to contact me at (609) 818-4732 or Nandan Mavinkurve at (609) 818-5386.

Sincerely,

Bristol-Myers Squibb Company

William J. Regan
Director
CMC – Marketed Products, North America

Enclosures

Cc: Food and Drug Administration
North Brunswick Office
120 North Center Drive
North Brunswick, NJ 08902

Desk copy: Mr. Ernest Papas
Division of Dermatologic and Dental Drug Products (HFD 540)

APPEARS THIS WAY
ON ORIGINAL

(30)

# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax 609 252-6000

April 24, 2000

**Kathy B. Schrode, Ph.D.**
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science


NDA ORIG AMENDMENT

**NDA 21-145**
**Vaniqa™ (eflornithine hydrochloride 15% cream)**

Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

BZ

## RESPONSE TO INFORMATION REQUEST

Dear Dr. Wilkin:

Reference in made to our NDA 21-145 for Vaniqa™ (eflornithine hydrochloride 15% cream) and to the information requests sent by FDA by FAX on March 8, 2000 and April 10, 2000.

We are pleased to provide responses to the five statistical and clinical questions of March 8 and the 4th question (Intent-to-Treat population) of April 10, as follows:

1. A subset analysis of patients who got worse: Results are summarized in Table 1 for data in Appendices 1.1 and 1.2. A statistical superiority of eflornithine HCl 15% cream over its vehicle was observed (p-value <0.05) at all visits during the treatment period.

2. An analysis of efficacy results by center: Results are summarized in Tables 2 and 3 for data in Appendices 2.1 and 2.2. For all sites in study DE140-001 and 8 of 9 sites in study DE140-002, Vaniqa™ had higher or equal success rates relative to vehicle at week 24. Similar results were observed in an Intent-to-Treat (missed visit considered as failure) data set included as Appendices 2.3 and 2.4.

3. A pivotal trials subset analysis for Caucasians and African Americans: Results are summarized in Table 4 for data in Appendices 3.1 to 3.3. Overall, there were no clear differences between Caucasians and African Americans or between African Americans in each study. Consistent results were observed in an Intent-to-Treat (missed visit considered as failure) data set included as Appendices 3.4 to 3.6.

4. Details on the circumstances of investigator evaluation and timing of photographs: A narrative is attached as an appendix. It includes an analysis of the number of skin adverse event evaluations that may have been impacted by a protocol deviation concerning the assignment of investigator evaluator. It also concludes that only one subject had photographs taken at the initial visit rather than at +48 hours.

5. A SAS listing of subjects who had skin related adverse events: A listing of skin related AEs is provided, as hard copy and on diskette, that shows site number, patient number, primary term, treatment code, AE code, relative days since 1st dose, AE intensity, and AE duration.

We are currently preparing a response to your request of April 17 for an additional table and expect it to be available shortly. Likewise, we are attempting to secure copies of the relevant statistical programs for your use.

If I can be of any further assistance in connection with this application, please feel free to contact me by FAX at (609) 252-6000 or by telephone at (609) 252-6463.

Sincerely yours,

Kathy B. Schrode

Kathy B. Schrode
Group Director, Life Style Products
FDA Liaison and Global Strategy Unit

Attachments

Desk Copy: Mill[illegible] Wright, Project Manager

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science



**GENERAL CORRESPONDENCE**
**REQUEST FOR TELECONFERENCE**

**NDA 21-145**
**Vaniqa™ (eflornithine HCl, 15% cream)**

March 28, 2000

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and
Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20850

Dear Dr. Wilkin,

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine HCl, 15% cream). We would like to request a teleconference with the chemistry reviewer to discuss the following items:

- Addition of an additional manufacturing site for finished product.
  We would like to discuss the possibility of adding our manufacturing facility in Humacao, PR as an additional site to manufacture finished product.
- Addition of [redacted]
  What type of data does the Agency need to support this?
- Update to [redacted] protocol in [redacted] DMF [redacted]

BMS participants in this teleconference will include:

William Regan, Director. Regulatory Science
Nandan Mavinkurve, Associate Director, Regulatory Science
Kathy Schrode, Group Director, Regulatory Science

ORIGINAL

We would like to have the teleconference as soon as possible; 15-30 minutes is anticipated as the needed time. Suggested dates and times are:

March 29 in the afternoon
March 30 9-11 am or 2-5 p.m
Week of April 3 - anytime, any day except April 3.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
Regulatory Science

Desk Copy: M. Wright (via fax)

APPEARS THIS WAY
ON ORIGINAL

(16)

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6463 Fax: 609 252-6000

Kathy B. Schrode, Ph.D.
Group Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science



**GENERAL CORRESPONDENCE**

**NDA 21-145**
**Vaniqa™ (eflornithine HCl, 15% cream)**

NDA DRUG AMENDMENT

March 28, 2000

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and
Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20850

BM

Dear Dr. Wilkin,

Reference is made to our NDA 21-145 for Vaniqa™ (eflornithine HCl, 15% cream).

When reviewing our clinical data we discovered an additional pregnancy that occurred during the clinical trials, Subject #915 in the DE140-002 study (vehicle group). Attached is an updated report on the outcome of all of the pregnancies which occurred during clinical trials of eflornithine hydrochloride, 15% cream.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director, Life Style Products
Regulatory Science

Attachments
Desk Copy: M. Wright (via fax)

ORIGINAL

(45)

WESTWOOD-SQUIBB COLTON HOLDINGS PARTNERSHIP
777 Scudders Mill Road
Princeton, New Jersey 08536

NDA ORIG AMENDMENT

**AMENDMENT TO A PENDING NDA:**
REVISED DRAFT LABELING

March 2, 2000

BL

**NDA 21-145**
**Vaniqa™ (eflornithine HCl, 15% cream)**

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
HFD-540
Document Control Room
Office of Drug Evaluation V
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr Wilkin,

Reference is made to the original submission of NDA 21-145 for Vaniqa™ (eflornithine HCl, 15% cream). This submission provides a number of revisions to the proposed draft labeling originally submitted to this NDA. These proposed changes clarify the language describing the indication and the summary of overdosage information, note the new address of the Westwood-Squibb business offices, and correct typographical errors in the tube and carton labeling.

No new clinical data are cited in this amendment. These proposed labeling changes merely seek to clarify the originally proposed language.

The electronic documents provided in this submission were prepared and organized in conformance with the 1999 guidance on provision of regulatory submissions in electronic format. The cover letter, Form 356h and table of contents are provided in both paper and electronic format. The electronic portion of the submission consists of 15 files and 4 folders on one CD-ROM disk which is being sent to the Central Document Room. The total size of the electronic submission is less than 5.4 Mb. The files were screened for known viruses on March 3, 2000, with Norton Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected.



ORIGINAL

For the convenience of reviewers, those documents in the submission that are in electronic form contain hypertext links to other documents referenced within the text and tables. These hyperlinks for file names appear in blue type in the electronic document. Document names used in these tables generally conform to the scheme outlined in the FDA guidance. There are minor differences, however. For example, each of the packaging components is in a separate file, identified by the size and type of container.

Please note that some electronic files are not specifically outlined in the guidance, but are included to clarify information in the submission. The electronic table outlining the labeling history, labeling/history.pdf, includes a hyperlink to a document (N21145/labeling/changes.pdf) which identifies each of the proposed changes in the package insert, and a discussion of the rationale supporting these changes (N21145/labeling/support.pdf). The file labeling/current.pdf includes the package insert which was provided in the original submission. The proposed package insert is provided in both Word97 (".doc") and Adobe Acrobat (".pdf") formats. Acrobat files of tube and carton labeling, incorporating the requested changes, are linked to the labeling history document. As the labeling is not yet approved, we have not designated a file as the approved package insert.

If you should require any further information on this application, please do not hesitate to contact me by phone at (609) 252-6463 or by FAX at (609) 252-6000.

Sincerely,

Kathy B. Schrode, Ph.D.
Group Director, Life Style Enhancement
Regulatory Sciences

APPEARS THIS WAY
ON ORIGINAL

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 Page 2*

FOR FDA USE ONLY
APPLICATION NUMBER

**APPLICANT INFORMATION**

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Westwood-Squibb Colton Holdings Partnership | March 2, 2000 |
| TELEPHONE NUMBER *(Include Area Code)* (609) 252-6463 | FACSIMILE (FAX) NUMBER *(Include Area Code)* (609) 252-6000 |
| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP code or Mail Code, and U.S. License number if previously issued)*: 777 Scudders Mill Rd. Princeton, NJ 08536 | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP code, telephone & FAX number)* IF APPLICABLE |

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 21-145

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Eflornithine hydrochloride | VANIQA |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* difluoromethyl-D,L-ornithine monohydrochloride | CODE NAME *(if any)* BMS-203522 |

DOSAGE FORM: Cream | STRENGTHS: 15% | ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of unwanted excessive facial hair in women

**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, 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

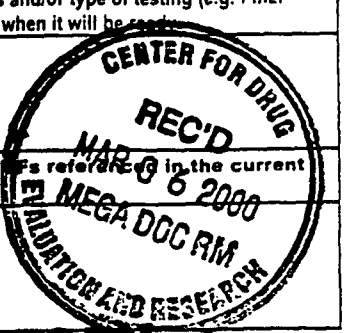
REASON FOR SUBMISSION: Revised proposed labeling

PROPOSED MARKETING STATUS (Check one) ☒ PRESCRIPTION DRUG PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ 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.




**Cross references (list related License applications, INDs NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)**

IND _____ BMS-203522 – Bristol-Myers Squibb
DMF _____ Facilities and Controls - Westwood-Squibb Pharmaceuticals Inc.
NDA 19-879 Omidyl – Marion Merrell Dow



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| 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 control section (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)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| | 9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| | 10. Statistical section (21 CFR.314.50 (d) (6), 21 CFR 601.2) |
| | 11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| | 12. Case reports forms (CFR 314.50 (f) (1), 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 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form 3397) |
| √ | 19. OTHER *Specify)*<br>Electronic copy of labeling, cover letter. Form 356h |

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all 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 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.
5. Regulations on reports in 21 CFR.314.80, 314.81, 600.80 and 600.81.
6. 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 |
|---|---|---|
| Kathy B. Schrode | Kathy B. Schrode, Group Director | 3/2/2000 |

| ADDRESS *(Street, City, State, Zip Code)* | Telephone Number. |
|---|---|
| 777 Scudders Mill Road, Princeton, New Jersey 08536 | (609) 252-6463 |

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