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

Worldwide Regulatory Affairs

B2

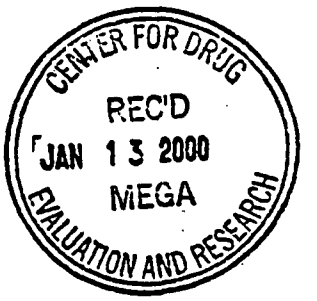
NDA

RESPONSE TO FDA REQUEST FOR INFORMATION

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

January 12, ~~1999~~ 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 Information Request, dated November 22, 1999 from Millie Wright, Project Manager.

In response to that request, we are providing the following information in electronic and/or hard copy format, as indicated.

Biopharmaceutics (PK)

1. Paper copies of the references numbered 10 through 18 from the Clinical Pharmacology Summary are provided as requested.

Biostatistics

1. SAS Data Sets for the pivotal efficacy studies [DE140-001 and DE 140-002] and one open-label safety study [DE-140-010] have previously been provided to you. CD-ROMs are enclosed containing SAS Data Sets for the clinical pharmacology study [DE140-003] and the other open label safety study [DE-140-011]. The file noted as "fmtpdf.xls" on the DE140-003 CD-ROM provides information on the contents of the four SAS files for that study. A one-page attachment lists the variable name definitions.

ORIGINAL

2. The SAS Data Set for the dermal carcinogenicity study (Study 455-032) is provided on a 3.5" diskette. The ReadMe.doc file, also on the diskette, provides information on data field labels. A hard copy of the ReadMe.doc file is attached.

Clinical

1. We are providing, in hard copy, a detailed Table of Contents (TOC) for Volume 1.2. The pagination of this volume in the original submission is correct, although a collating error resulted in duplicate numbering of some sections.

2. & 3. One diskette is enclosed that contains a Zipped file (Dfmodocs.zip) that, upon extraction, will provide the following requested information in MS Word format:

d140001f.doc - Text and tables for DE-140-001 (Pivotal Efficacy Trial)
d140002f.doc - Text and tables for DE-140-002 (Pivotal Efficacy Trial)
Dfmoiss&ise.doc - Integrated Summary of Safety and Efficacy
ISSEAPPENDIX1.doc - Appendix1 – Serious Adverse Events Narratives
ISSEAPPENDIX2.doc - Appendix2 – Pregnancy Narratives

Another diskette is enclosed that contains, in MS Word format, those sections of the Application Summary in Volume 1.2 that are available in an electronic format:

App Sum Vol 1.2.2-16.doc	Overview
App Sum Vol 1.2.17-28.doc	Tabular Summaries
	[Note: Pages 29-74 are Report Synopses which can be supplied, if requested.]
App Sum Vol 1.2.75-115.doc	Efficacy
App Sum Vol 1.2.116-212.doc	Safety
App Sum Vol 1.2.213-216.doc	Overdosage
App Sum Vol 1.2.217-227.doc	Risk / Benefit

4. Studies conducted under protocols [redacted] address [redacted] Vaniqa® (eflornithine HCl, 15% Cream) [redacted] These protocols were submitted to IND [redacted], which addresses [redacted]. For reference, copies of the Overview and Rationale for these [redacted] are included. For completeness, protocol amendments (administrative letters), which clarify some of the information in these protocols, are also included. Efficacy data from these studies are irrelevant to the female hirsutism claim, but interim blinded safety data have been included in the Integrated Summary of Safety and Efficacy in NDA 21-145 (Vol.1.137.20 through Vol.1.137.26).

5. Included in this submission are copies of the photographs which were used for training the physicians on the use of the Physician's Global Assessment scale. These photographs clearly display the level of improvement expected for each score. In the conduct of the study, a subject's photographs could be used as an aid in determining the PGA. However, as discussed with the FDA during the design of the protocol, it was felt that the limited hair growth since the shave (48 hours) was best assessed in person, where changes in the angle of the light and feel of the hair could be used in the evaluation, rather than from photographs.

The following table outlines the photographs included in this submission. For each subject, a pair of photographs is provided, one at baseline and one at end of treatment (24 weeks). For several subjects, two pairs of photographs are provided, one centering on the neck and one on the chin and lower face.

Subject #	Site	Degree of improvement
—054	Chin	Clear/ almost clear
	Neck	"
—106	Chin	Clear/ almost clear
	Neck	"
—013	Chin	Marked improvement
	Neck	"
—038	Chin	Improved
	Neck	"
—168	Neck	Improved
—171	Chin	Improved
—001	Neck	No improvement/worse
—026	Neck	No improvement/worse

The media for this electronic submission has been prepared as follows: The total size of the electronic submission is approximately 21.6 MB. There are a total of 8 files. The files were checked for viruses on January 7, 2000 with Norton Antivirus Software (Version 5.01.1 for Windows NT 4.0) and no viruses were detected. The electronic review aid has been provided on 2 CD-ROM disks.

APPEARS THIS WAY
ON ORIGINAL

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,

David L Shlueter for KBS

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

KBS/DS/dk

CC: Millie Wright, Project Manager [Archival and Clinical Copies]

APPEARS THIS WAY
ON ORIGINAL

Table of Contents

Biopharmaceutics (PK)

References from Clinical Pharmacology Summary

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Company	January 12, 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

CENTER FOR DRUG REC'D JAN 13 2000 MEGA EVALUATION AND RES

PRODUCT DESCRIPTION

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

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:	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, 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, OR AADA, 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

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

NUMBER OF VOLUMES SUBMITTED [redacted] 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)

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 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 FDA Request for Information

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
[redacted]	Kathy B. Schrode, Ph.D., Director, Regulatory Sciences	January 12, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 4000, Princeton, NJ 0854[redacted]000	(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.

FORM FDA 356h (7/97)

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

ORIGINAL
NC

GENERAL CORRESPONDENCE - REQUESTED DOCUMENTS

NEW CORRES

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

October 15, 1999

Jonathan Wilkin, M.D., 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 Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 21-145 for VANIQA (eflornithine hydrochloride cream) 15%, and to a telephone request on October 14, 1999, from Ms. Mildred Wright, Project Manager for this NDA. Ms. Wright requested additional desk copies of selected volumes of the NDA. These are being sent under separate cover. Ms. Wright also requested a copy of the proposed draft labeling for VANIQA Cream in electronic format. This submission provides the proposed package insert and Patient Information Leaflet text in electronic format. A 3.5" computer disk, incorporating the proposed texts for the product in Word97 format is provided directly to Ms. Wright in a desk copy of this amendment, to ensure prompt delivery to the reviewers.

The text of the labeling provided in electronic format is identical to that submitted in the NDA. However, some graphical elements (i.e., chemical structure or special characters) may not be faithfully reproduced between computer systems. The printed text provided in the original NDA is to be relied upon in case of any such differences.

If there are any questions regarding the information provided in this submission, please contact the undersigned at (609) 252-4317, or via fax at (609) 252-7396. I can also be reached via electronic mail at "David.Silberstein@bms.com".

Sincerely,

David L. Silberstein
Manager
Worldwide Dossier Planning and Management

DLS/dk
Desk Copy: M. Wright, HFD-540, Room N243 (w/ diskette)

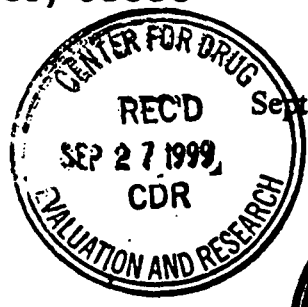
APPEARS THIS WAY
ON ORIGINAL

(27)

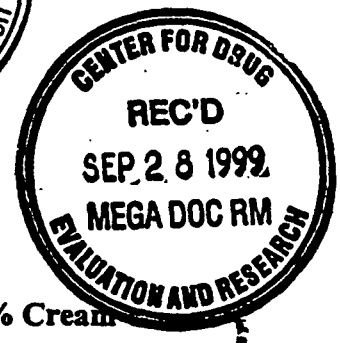
VOL.1.1.5

WESTWOOD-SQUIBB COLTON HOLDINGS PARTNERSHIP

777 Scudders Mill Road
Princeton, New Jersey 08536



September 24, 1999



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room, Room 214
12420 Parklawn Drive
Rockville, MD 20852

RE: **Original NDA 21-145**
Eflornithine Hydrochloride 15% Cream

Dear Dr. Sir or Madame:

In accordance with Section 505(b) of the Federal Food, Drug, and Cosmetic Act and Part 314 of Title 21 of the Code of Federal Regulations, Westwood-Squibb Colton Holdings Partnership hereby submits this NDA for a topical cream product containing 15% eflornithine hydrochloride. This application provides clinical, nonclinical, and chemistry manufacturing and controls information to demonstrate safety, efficacy, and quality of eflornithine hydrochloride 15% Cream for the treatment of excessive female facial hair.

The majority of the clinical and nonclinical data presented in this NDA were generated in the United States by Bristol-Myers Squibb under IND —— Additional studies were performed in Europe, South Africa, Australia, and Mexico. This information was also submitted under IND —— Early development information was obtained under IND —— Prior FDA approval of an intravenous route of administration for this was obtained by a separate Sponsor under NDA 19,879.

A summary of relevant correspondence with the Agency during the clinical development of the product, notes to the reviewers, and appropriate information to address requirements related to user fees, patent information, debarred persons, financial interest of investigators, field copies, NDA access authorization letters, and Drug Master File authorization letters have been included in the appropriate sections of this NDA.

The [redacted] will be manufactured by the [redacted] The drug active manufacturing sites are ready for inspection at this time. However, as is noted in the filing, we intend upon executing a geography-only change for early steps of the drug active synthesis from [redacted] either early in the review process or immediately upon approval. The plant will be ready for inspection of these early steps and equipment – that are not yet part of this NDA filing – December 1, 1999. FDA may wish to inspect for all steps after the December 1, 1999 date to maximize resource utilization.

The text of many sections of this NDA can be made available to the Agency upon request, on 3.5" diskettes, using Word. SAS datasets of the clinical data have been provided on CD-ROM concurrent with this application.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7680, by Fax at 716-887-3638, or by Internet Mail at schrodek@bms.com.

Sincerely,

Kathy B. Schrode, Ph.D.
Director, World Wide Regulatory Affairs
Bristol-Myers Squibb Pharmaceutical
Research Institute for
Westwood-Squibb
Colton Holdings Partnership

[redacted]

APPEARS THIS WAY
ON ORIGINAL

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

Phase IV CMC Commitment

Bristol-Myers Squibb Company agrees to add a test for ——— of the product to the stability storage testing program. Data will be collected for the first three commercial lots over the approved shelf-life (24 months). The collected data for these three lots will be analyzed and submitted to the Agency for review within four months of completion of the 24 month stability study for the third lot. If the data indicate a ——— a ——— would then be required.

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

FAXED 7/27/00

Date: July 27, 2000

To: Bill Regan
WestWood Squibb Colton Holdings Partner
Phone: (609) 818-4732
Fax: (609) 818-5832

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

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Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: July 27, 2000

Subject: Phase 4 Commitment

Hi Bill,
Attached is the Phase 4 commitment.

Millie

cc
NDA 21-145
HFD-540/Wright

APPEARS THIS WAY
ON ORIGINAL

Phase 4 CMC Commitment:

BEGIN

The Applicant agrees to add a test for [redacted] of the product to the stability storage testing program. Data will be collected for the first three commercial lots over the approved shelf-life (24 months). The collected data for theses three lots will be analyzed and submitted to the Agency for review within four months of completion of the 24 month stability study for the third lot. If the data indicate a [redacted], a [redacted] would then be required.

/S/ 7/26/00

/S/ 7/26/2000

END

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

07/27/00 15:13

NO.	MODE	BOX	GROUP
597	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
07/27 15:12	00'34"	609 818 5832	003/003	OK		0000

FDA Fax Memo

Date: July 27, 2000

To: Bill Regan
WestWood Squibb Colton Holdings Partner
Phone: (609) 818-4732
Fax: (609) 818-5832

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memo

URGENT

FAXED 7/24/00

Date: July 24, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

URGENT

FDA Fax Memo

Date: July 24, 2000

Subject: Wording for label

Hi Kathy,

The wording should be as follows:

"Vaniqa statistically significantly reduced how bothered patients felt by their facial hair and by the time spent removing, treating, or concealing facial hair. These patient-observable differences were seen as early as 8 weeks after initiating treatment. Hair growth approached —— within 8 weeks of treatment withdrawal."

I will send fax with attendees later.
Millie

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

07/24/00 14:03

NO.	MODE	BOX	GROUP
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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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FDA Fax Memo URGENT

Date: July 24, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

FDA Fax Memo

Date: July 18, 2000

FAXED 7/18/00

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 5 pages (including this page)

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Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: July 18, 2000

Subject: Proposed label for NDA 21-145/Vaniqa Cream

Hi Kathy,

Attached you will find the Division proposed label. Please review. If you have questions, we can schedule a t-con to discuss them. (The insertion that I mentioned during the t-con can be found on line 81.)

Respectfully,
Millie

cc
Orig NDA 21-145
HFD-540/Div File
HFD-540/Wright

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 10 PAGE (S)

Draft

Labeling

MESSAGE CONFIRMATION

07/18/00 17:21

NO.	MODE	BOX	GROUP
532	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
07/18 17:18	03'33"	609 252 6000	012/012	OK		0000

FDA Fax Memo

Date: July 18, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 12 pages (including this page)

NDA 21-145/June 23 fax

FDA Fax Memo

FAXED 6/23/00

Date: June 23, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 5 pages (including this page)

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Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: June 23, 2000

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

We would like to schedule a t-con to discuss the following chemistry information requests that were identified during the review. The topics to be discussed are the following:

WITHHOLD 2 PAGE (S)

If you have questions, please call.

Respectfully,
Millie

CC:
Orig NDA 21-145
HFD-540 Div File
HFD-540/M.Wright

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

06/23/00 13:00

J.	MODE	BOX	GROUP
407	TX		

DATE/TIME	TIME	DISTANT STATION 'D	PAGES	RESULT	ERROR PAGES	S.CODE
06/23 12:59	01'11"	609 252 6000	005/005	OK		0000

NDA 21-145/June 23 fax

FDA Fax Memo

Date: June 23, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

[redacted] transmission includes 5 pages (including this page)

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FDA Fax Memo

FAXED 6/7/00

Date: June 7, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: June 7, 2000

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

The medical reviewer requests the following information:

Please provide forms 4354 concerning financial disclosure for the investigators of the open-label trials, DE140-010 and DE140-011.

Thanks,
Millie

CC:
Orig NDA 21-145
HFD-540/Wright

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

06/07/00 12:08

NO.	MODE	BOX	GROUP
297	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
06/07 12:07	00'27"	609 252 6000	002/002	OK		0000

FDA Fax Memo

Date: June 7, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

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cc
NDA 21-145
HFD-540/Wright

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 CORPORATE BOULEVARD, HFD-540
ROCKVILLE, MD 20850

FAXED 5/30/00

FACSIMILE TRANSMISSION RECORD

DATE: 5/30/00 Pages (including cover) (1)
TO: Kathy Schrode
COMPANY: BMSquibb
ADDRESS:
FAX PHONE#: 609-252-6000 Our Fax # (301) 827-2075
Voice # (301) 827-2020

Kathy: Re: NDA 21-145, Vaniqa - The clinical reviewer needs the following information:
(1) The data on the 13 subjects in Study DE140-010 who had elevated LFTs (ref. volume 1.120.90), and the results for all visits.
(2) The same data as above for the 17 subjects with elevated LFTs in study DE140-011 (ref. volume 1.85.95).
(3) The same type of information as above for all patients who had neutropenia/leukopenia (who went from normal to low), and the results of all visits. For these patients, she would also like to know the ethnicity.
She would like this information as soon as possible.
Thanks.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: /S/
TITLE: CSO Tech.
TELEPHONE: 301-827-2061

MESSAGE CONFIRMATION

BEST POSSIBLE COPY

05/30/00 09:21

	MODE	BOX	GROUP
232	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
05/30 09:21	00'25"	609 252 6000	001/001	OK		0000

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 CORPORATE BOULEVARD, HFD-540
ROCKVILLE, MD 20850

FACSIMILE TRANSMISSION RECORD

DATE: 5/30/00 **Pages (including cover)** (1)

TO: Kathy Schroeder

COMPANY: BMS Squibb

ADDRESS:

FAX PHONE#: 609-252-6000 **Our Fax # (301) 827-2075**

Voice # (301) 827-2020

Kathy: Re: NDA 21-145, Vaniqa - The clinical reviewer needs the following information:
(1) The data on the 13 subjects in Study DE140-010 who had elevated LFTs (ref. volume 1.120.90), and the results for all visits.
(2) The same data as above for the 17 subjects with elevated LFTs in study DE140-011 (ref. volume 1.85.95).
(3) The same type of information as above for all patients who had neutropenia/leukopenia (who went from normal to low), and the results of all visits. For these patients, she would also like to know the ethnicity.
She would like this information as soon as possible.

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 3/22/00

TO:

Name Kathy Schrode

Fax No. 609 252-6000

Phone No. _____

Location GMS

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

Comments: NDA 21145 VANIQA

Could you please send the study reports for items

#14 - #15 - #16 listed in vol 1.32.42 and

#17 - #18 listed in vol 1.32.43 per Stephanie Reviewer request.

Thanks

/S/

9. Malhotra BK. Toxicokinetic analysis of BMS-203522 in a dermal carcinogenicity study in mice (Study 96701). Bristol-Myers Squibb Pharmaceutical Research Institute 1999; Report no. 920000003.

10. Malhotra BK and Musick T. Effectiveness of dermal tape stripping to determine percutaneous absorption and preliminary pharmacokinetics of [^{14}C]BMS-203522 in rats following single or twice-daily dermal doses and single oral doses. Bristol-Myers Squibb Pharmaceutical Research Institute 1999; Report no. 920000133.

11. Malhotra BK and Musick T. Absorption, excretion, and tissue distribution of [^{14}C]BMS-203522 in SP106A following twice-daily dermal administration and [^{14}C]BMS-203522 in solution following single daily oral administration for 7 days to female rats. Bristol-Myers Squibb Pharmaceutical Research Institute 1999; Report no. 920000135.

12. Shander D, Ahluwalia GS, and Gale, MR. *In vitro* permeation studies. *In:* Inhibition of hair growth by DL-α-difluoromethylornithine (DFMO). Gillette Research Institute Report 1988.

13. Ahluwalia GS and Harrington FE. *In vitro* permeation of DFMO in guinea pig skin (GMEA study no. 7766). Gillette Research Institute Report 1991.

14. 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.

15. [redacted] 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.

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

Request 14-18 Study report

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

18. 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.

19. Haegele KD, Alken RG, Grove J, Schechter PJ, and Koch-Weser J. Kinetics of α-difluoromethylornithine: An irreversible inhibitor of ornithine decarboxylase. Clin. Pharmacol. Ther. 30:210-217;1981.

20. Abeloff MD,. Slavik M, Luk GD, Griffin CA, Hermann J, Blanc O, Sjoerdsma A, and Baylin SB. Phase I trial and pharmacokinetic studies of α-difluoromethylornithine- an inhibitor of polyamine biosynthesis. J. Clin. Oncol. 2: 124-130; 1984.

21. Love RR, Carbone PP, Verma AK, Gilmore D, Carey P, Tutsch KD, Pomplun M, and Wilding G. Randomized phase I chemoprevention dose-seeking study of α-difluoromethylornithine. J. Natl. Cancer Inst. 85: 732-737; 1993.

22. Pendyala L, Creaven PJ, and Porter CW. Urinary and erythrocyte polyamines during the evaluation of oral alpha-difluoromethylornithine in a phase I chemoprevention clinical trial. Cancer Epidemiology, Biomarkers & Prevention 2:235-41;1993.

23. D[illegible] B. and Morris T. Physiological parameters in laboratory animals and h[illegible]ns. Pharm. Res. 10:1093-1095;1993

24. Rowland M and Tozer TN. Elimination. *In:* Clinical Pharmacokinetics: Concepts and Applications, 3rd ed., Lea and Febiger, PA, pp. 156-183; 1995

MESSAGE CONFIRMATION

05/22/00 16:24

NO.	MODE	BOX	GROUP
184	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
05/22 16:23	00'54"	609 252 6000	003/003	OK		0000

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 5/22/00

TO:

Name Kathy Schrade

Fax No. 609 252-6000

Phone No. [redacted]

Location [redacted]

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

FDA Fax Memo

FAXED 4/17/00

Date: April 17, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: April 17, 2000

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

Dr. Li has an addition request. The request is for both studies DE14001 and DE14002. Please summarize subject accounting information into the following table.

	Eflornithine 15%		Vehicle	
	n	%	n	%
Randomized				
Received medication				
Complete 24 wks				
Complete 32 wks				
Discontinued before Wk 24				
Death				
Due to AE				
Due to lack of efficacy				
Lost to follow-up				
Others				

Respectfully,
Millie

CC:
Orig NDA 21-145
HFD-540/Wright

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

04/17/00 09:28

NO.	MODE	BOX	GROUP
934	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
04/17 09:27	00'28"	609 252 6000	002/002	OK		0000

APPEARS THIS WAY
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FDA Fax Memo

Date: April 17, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

FDA Fax Memo

FAXED 4/10/00

Date: April 10, 2000

To: Kathy B. Schrode, Ph. D/Lisa
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: April 10, 2000

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

We would like to schedule a t-con to discuss the following statistical questions:

1. In video image data set via.xpt for Study DE140001, 87 subjects in vehicle and 160 in eflornithine had hair length data for week 24, while in study report there were only 77 subjects in vehicle and 128 in eflornithine (vol 1.51, p99).

2. Similar discrepancy also existed in Study DE140002. 92 in vehicle and 178 in eflornithine in data set vs. 77 in vehicle and 151 in eflornithine in study report.

3. Where is the baseline data for video image hair length located in the submission?

4. In the primary analysis of the primary efficacy variable (PGA), the analysis did not include all the ITT population (or ASR). The Division would like to include all the subjects that are randomized in the analysis and classify those who did not have assessment at Week 24 as failure.

My statistical and clinical reviewers are available Wednesday, April 12th at 2 PM (our time). Would that time work for your reviewers?

Respectfully,
Millie

CC: Orig NDA 21-145/HFD-540/Div File/HFD-540/Wright

APPEARS THIS WAY
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MESSAGE CONFIRMATION

04/10/00 08:30

NO.	MODE	BOX	GROUP
887	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
04/10 08:30	00'31"	609 252 6000	002/002	OK		0000

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: April 10, 2000

To: Kathy B. Schrode, Ph. D/Lisa
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

HFD-540
M. Wright

FDA Fax Memo

Date: March 8, 2000

FAXED 3/8/00

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 2 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: March 8, 2000

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

During a clinical and statistical team meeting, for Vaniqa, reviewers identified the following information requests:

Please provide:

1. A subset analysis of patients who got worse.
2. An analysis of the efficacy results by center.
3. For the 2 active arms of the studies, provide a subset analysis of efficacy between Caucasians and African Americans and also between African Americans in each study.
4. The following information:
   a. Which centers did not use different investigators to evaluate Physician's Global and adverse events.
   b. Identify the two centers where the photographs were taken at the initial rather than the 48 hour visits in Study DE140-001.
5. A list of subjects in SAS format who had skin related adverse events. In this list, please include the information regarding the relative date of on site (time since applying study medications), severity, duration and symptom by preferred term and code. Multiple records for one subject are acceptable.

If you have questions, please call.

Respectfully,
Millie

CC:
Orig NDA 21-145
HFD-540 Div File
HFD-540/M.Wright

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

03/08/00 21:49

NO.	MODE	BOX	GROUP
653	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
03/08 21:48	00'31"	609 252 6000	002/002	OK		0000

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: March 8, 2000

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

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FDA Fax Memo

Date: November 22,1999

Subject: Information request for NDA 21-145/Vaniqa (eflornithine HCL, 15% Cream

Hi Kathy,

During our filing meeting for Vaniqa, the following information requests were identified:

Biopharmaceutics (PK)

1. Please submit copies of references #10-18 in human PK section of the application. (I had already requested copies earlier during a t-con with you.)

Biostatistical

1. Electronic submission of the data has not been provided. Electronic submission of the data (SAS data sets) and a data dictionary is essential. Please provide SAS data sets with all relevant information for the two phase 3 Studies: DE 140-001 & 002; plus possibly DE 140-010, 011, & 003. Annotated case report forms make excellent codebooks, especially if the algorithms for all derived variables are included. For additional information, please refer to Guidance Document, IT 3--Guidance for Industry: Providing Regulatory Submissions in Electronic Format—NDAs. The web site address where you can obtain a copy of the document is www.fda.gov/cder/guidance/index.htm

2. Also, please provide SAS data sets for the dermal carcinogenicity study (and any other carcinogenicity studies). Attached you will find the Guidance Document, Formats and Specifications for Submission of Animal Carcinogenicity Study Data.

APPEARS THIS WAY
ON ORIGINAL

Clinical

1. Please provide a more detailed table of contents for Volume 1.2.
2. Please provide, in MS Word format, the text and tables for the pivotal efficacy trials and summary of Volume 1.2.
3. Please provide, in MS Word format, the integrated summary of efficacy and safety, located in Volumes 1.36 & 1.37.
4. In Volume 1.1, in the table on page 80, studies [redacted] are listed. These studies are not listed in the index. Where are they located in the submission? What are they?
5. How long would it take for you to provided the Division with clinical photographs, in a reviewable format, to correlate with the primary efficacy variables?

I will call you to establish your projected timelines and to answer any questions that you may have.

Respectfully,
Millie

Attachment (1)

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ESSAGE CONFIRMATION

11/22/99 16:49

O.		BOX	GROUP
932			

DATE	E	T	E	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
11/2	6:45		'09"	609 252 6000	016/016	OK		0000

FDA Fax Memo

Date: November 22, 1999

To: Kathy B. Schrode, Ph. D
Director, World Wide Regulatory Affairs
WestWood Squibb Colton Holdings Partner
Phone: (609) 252-6463
Fax: (609) 252-6000

From Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 16 pages (including this page)

WITHHOLD 3 PAGE (S)

Draft

Labeling