

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: **20-574**

CORRESPONDENCE

COMPLETED



February 7, 1995

Drug Master File Staff
Food and Drug Administration
Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

RE: Update of (Type II) DMF [redacted]
Clotrimazole [redacted]
DMF Holder: [redacted]
Appointed Agent: [redacted]

Dear Sirs:

[redacted] as appointed agent, hereby submits an update to Drug Master File [redacted] for clotrimazole. For your convenience, a listing of each revision, along with any necessary justifications, is provided. There have been no changes to the basic manufacturing process.

Enclosed is a stamped, self-addressed envelope and an extra copy of this cover letter. Please date stamp the letter and return [redacted] as confirmation of receipt.

If you have any questions concerning this update, please contact [redacted]
[redacted]

Sincerely yours,

[Large redacted signature block]

Vice President Regulatory Affairs
[redacted]
[redacted]

NDA 20-574

John M. Clayton, Ph.D.
Senior Vice President
Scientific and Regulatory Affairs
Schering-Plough HealthCare Products
110 Allen Road
Liberty Corner, NJ 07938

JUN 14 1995

Dear Mr. Clayton:

We have received your new drug application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Product: Gyne-Lotrimin 3 3-Day Vaginal Cream

Date of Application: April 27, 1995

Date of Receipt: April 28, 1995

Our Reference Number: NDA 20-574

Unless we find the application not acceptable for filing, the filing date will be June 28, 1995.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact:

Christina H. Chi, Ph.D.
Project Manager
(301) 443-0257

Sincerely yours,

/S/ 6/13/95

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Received Jan 29, 1996



Schering-Plough
HealthCare Products

Schering-Plough
Kenilworth, NJ
201-261-1000
1-800-438-0233
Telex: 353101
353101

January 26, 1996

Mary Fanning, M.D., Ph.D., FACP
Director, Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
HFD-520; Document Control Room 9201
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

**SUBJECT: NDA 20-574: Gyne-Lotrimin 3™ 3 Day Vaginal Cream
WITHDRAWAL OF UNAPPROVED APPLICATION**

Dear Dr. Fanning:

This is to notify you that we are hereby withdrawing our pending new drug application (#20-574) for Gyne-Lotrimin 3™ 3 Day Vaginal Cream without prejudice to refile as allowed under 21 CFR §314.65.

Sincerely,

A handwritten signature in cursive script, appearing to read 'J. Clark'.

Joseph D. Clark, Jr., Ph.D.
Vice President
Regulatory Affairs

Filed in duplicate
Desk copy: Dr. Christina Chi



April 9, 1997

Dr. Christina Chi
HFD-520
Corporate 2, Room S357
9201 Corporate Boulevard
Rockville, MD 20850
(301) 827-2125

RE: REQUEST FOR A MEETING

Dear Dr. Chi,

At your request, we are forwarding to you the specific topics which we would like to discuss at a meeting to be held at FDA involving representatives from both Taro Pharmaceuticals and Schering Plough.

Purpose

Schering and Taro wish to file a joint NDA for a 2% Clotrimazole Vaginal Cream. The purpose of this meeting will be to discuss the FDA requirements for filing such an NDA.

Specific Objectives

Schering and Taro seek guidance and support for a filing with two qualitatively identical 2% cream formulations, each of which has been shown as a three day treatment to be equivalent to the same standard, i.e., Schering's 1% Clotrimazole Cream used as a seven day treatment.

Agenda:

- 1) Brief review of the clinical and mycological result of both studies (15 min.).
- 2) Brief review of the two formulations utilized in the clinical studies (10 min.).
- 3) In vitro release data (10 min.).
- 4) Discussion of the specifics of compiling an NDA using Schering and Taro studies (25 min.).

Attendees from Schering and Taro

Schering Plough

Joe Clark, Ph.D.

John Clayton, Ph.D.

Taro Pharmaceuticals U.S.A., Inc.

Dan Moros, M.D.

Avraham Yacobi, Ph.D.

Terry Feldman, Ph.D.

Requested Participants from CDER:

Dr. David Feigal

Dr. Christina Chi

Dr. Renata Albrecht

Dr. Joseph Winfield

Dr. Eric Sheinin

Supporting documentation will be sent to CDER two weeks prior to the meeting.

We would like to propose as possible dates for this meeting: April 29, May 2, May 13, May 14, May 20 or May 21.

With many thanks for your effort.

Sincerely,



Avraham Yacobi, Ph.D.

President, Taro Research Institute

cc: Joe Clark, Ph.D.

June 4, 1997



Dr. Christina Chi
HFD-520
Corporate 2, Room S357
9201 Corporate Boulevard
Rockville, MD 20850
(301) 827-2125

**RE: AGENDA FOR CLOTRIMAZOLE 2% CREAM PRE-NDA MEETING
JUNE 18, 1997**

Dear Dr. Chi:

At your request, we are providing to you a brief summary of our presentation and copies of the slides to be used at the meeting scheduled for June 18, 1997, in which Taro Pharmaceuticals and Schering-Plough representatives will discuss the data to be used in support of a joint NDA for our two firms. Enclosed are 24 sets of copies, including a red three ring binder for your use.

The attendees from each company will be as follows:

Schering-Plough

Joseph Clark, Ph.D.
John Clayton, Ph.D.

Taro Pharmaceuticals U.S.A. , Inc.

Dan Moros, MD
Avraham Yacobi, Ph.D.
Terry Feldman, Ph.D.

The agenda for the meeting will be as follows:

1. Introduction and objectives of the Taro-Schering-FDA meeting (Dr. Moros, 5 minutes)
2. Brief review of the two formulations utilized in the clinical studies and the in-vitro release data (Dr. Feldman, 5 minutes)

3. Protocol design comparison of Schering and Taro studies (Dr. Clark, 5 minutes)
4. Brief review of clinical and mycological results of Schering study (Dr. Clark, 5 minutes)
5. Brief review of the clinical and mycological results of both studies (Dr. Moros, 5 minutes)
6. Discussion of the specifics of compiling an NDA using Schering and Taro studies (Dr. Clayton, 5 minutes)
7. Summary of Schering/Taro proposals (Dr. Moros, 5 minutes)
8. Question and answer period (Taro-Schering-FDA, 30 minutes)

We look forward to our meeting and wish to thank you once again for your kind assistance in arranging it on our behalf.

Sincerely,



Avraham Yacobi, Ph.D.
President, Taro Research Institute



Schering-Plough
HealthCare Products

July 8, 1997

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 604-1840

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Division of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

SUBJECT: Minutes of 6/18/97 FDA Meeting on Clotrimazole 2% Cream NDA

Dear Dr. Chi:

As discussed following the subject meeting, please find a copy of our minutes for the meeting. We request that in return you send us a copy of your minutes per MaPP 4512.1.

If you notice any significant differences in your understanding of the outcome of the meeting, please don't hesitate to call me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director
Regulatory Affairs

attachment



Schering-Plough HealthCare Products

Schering-Plough Corporation
110 Allen Road
P.O. Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1840
Fax (908) 604-1840

September 8, 1997

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
REQUEST FOR TELECONFERENCE**

Dear Dr. Chi:

Thank you for sending us a copy of the FDA minutes from the June 18, 1997 meeting to discuss a Taro/ Schering-Plough HealthCare Products (SPHCP) joint submission of a 3-day clotrimazole cream NDA.

As you know from our recent conversations, our plan is to conduct the "bridging" study discussed in the above referenced meeting to demonstrate therapeutic equivalence between the SPHCP and Taro formulations, and to re-open the withdrawn SPHCP NDA 20-574. The formula to be considered for OTC marketing approval will be the SPHCP formula. However, since this formula has not been previously marketed, we intend to include Taro's safety data for their formula, which has been marketed in Canada as an Rx product since 1988 and as an OTC product since 1995.

We would like to request a teleconference between the OTC Division and SPHCP/ Taro to further discuss items #6 and #7 in the "Discussion points and agreements reached" section of your minutes. These items pertain to the OTC Division's desire for 5 years of marketing experience prior to a product being marketed OTC and to the FDA's difficulty extrapolating Taro's safety experience to support SPHCP's product. Prior to this teleconference we will submit a list of the critical points of information which we feel support our position that the SPHCP formula is safe to receive direct OTC marketing approval. Since the bridge study is scheduled to begin this month, the timing of this teleconference is critical and your prompt

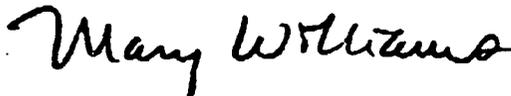
**Gyne-Lotrimin 3™ 3-Day Vaginal Cream
REQUEST FOR TELECONFERENCE**

Page 2

attention to this matter is greatly appreciated. Please contact me at (908) 604-1952 at your earliest convenience to discuss the arrangements.

Please be advised that the information contained in this submission is confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,



Mary E. Williams
Associate Director
Regulatory Affairs

TELEPHONE CONFERENCE CALL

September 29, 1997

1:15 PM - 2:15 PM

Schering-Plough HealthCare Products

Ronald J. Garutti, M.D.

**Vice President, Clinical Research/Regulatory
Affairs**

Walt Chambliss, Ph.D.

Vice President, Research & Development

Joseph D. Clark, Ph.D.

Consultant

Mary Williams

Associate Director, Regulatory Affairs

Taro Pharmaceuticals U.S.A., Inc.

Daniel A. Moros, M.D.

Vice Chairman

Lorraine W. Sachs, RAC

Senior Regulatory Affairs Scientist

Taro Pharmaceuticals Inc. (Canada)

Terry Feldman, Ph.D.

Vice President Research & Development

**APPEARS THIS WAY
ON ORIGINAL**



Schering-Plough
HealthCare Products

July 8, 1997

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 604-1840

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Division of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

SUBJECT: Minutes of 6/18/97 FDA Meeting on Clotrimazole 2% Cream NDA

Dear Dr. Chi:

As discussed following the subject meeting, please find a copy of our minutes for the meeting. We request that in return you send us a copy of your minutes per MaPP 4512.1.

If you notice any significant differences in your understanding of the outcome of the meeting, please don't hesitate to call me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director
Regulatory Affairs

attachment



Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604 -1640
Fax (908) 604 -1840

November 25, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
HFD 590;
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Subject: **RESUBMISSION**
NDA 20-574: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
(2% clotrimazole)

Dear Doctor Goldberger:

Schering-Plough HealthCare Products, Inc. (SPHCP) is herein resubmitting New Drug Application (NDA) 20-574 which was withdrawn without prejudice on January 29, 1996 prior to an action letter. Original NDA 20-574 is incorporated by reference in this resubmission which further supports the New Drug Approval of Gyne-Lotrimin 3™ 3-Day Vaginal Cream, a 2% clotrimazole antifungal cream, as an over-the-counter treatment of vulvovaginal candidiasis. A copy of the withdrawal letter and the Agency acknowledgment is attached. (Attachment #1 and #2).

As required by the Prescription Drug User Fee Act of 1992 (PDUFA) the remaining 50% of the user fee which is due upon withdrawal of a pending application was paid on March 6, 1996 (receipted copy of transmittal letter - Attachment #3). This resubmission is therefore not subject to additional fees as indicated in the Agency letter of February 12, 1996.

This resubmission is in essentially the same format as the original NDA as stipulated in 21CFR 314.50. It contains the results of a new pivotal clinical trial, a reanalysis of previously submitted clinical data, and other information which updates or revises information provided in the original NDA.

Agreements reached between the Agency and the Sponsor at meetings prior to submission of the original NDA were discussed in detail in the original submission and are summarized again in Section 8.B of this resubmission.

For the convenience of the reviewers, the summary volume of this resubmission has been completely revised to incorporate both original and new information and the remaining volumes provide only the new data and information. A detailed description of the format of this resubmission is included at the beginning of the index.

Following filing of the original NDA 20-574 on June 28, 1995, and based on a preliminary review, the medical reviewer, Joseph Winfield M.D., determined that only one of the identified pivotal clinical studies (#93-40) supported the effectiveness of 3-day 2% clotrimazole cream therapy. Therefore, on January 29, 1996 SPHCP withdrew NDA 20-574.

After withdrawal of NDA 20-574, the Sponsor met with representatives of the Division of Anti-Infective Drug Products (DAIDP) on April 3, 1996 and agreed upon a revised protocol for a new 3-day 2% clotrimazole cream study (minutes - attachment 4). Subsequent to this meeting, and before initiating the new study, SPHCP became aware of an existing clinical trial on a 3-day 2% clotrimazole cream which met the Agency criteria. SPHCP then acquired the rights to use the results of that clinical study (#95-50) conducted by Taro Pharmaceuticals U.S.A., Inc. (Taro). A statement confirming this agreement and signed by both parties is attached (#5).

The clinical trial design and evaluability criteria for the Taro study had previously been reviewed and agreed upon by the Agency at a meeting with Taro on September 12, 1996. [See Taro's minutes of this meeting (#6) as well as a January 9, 1997 letter (#7) from Dr. Feigal to Taro and the follow-up letter from Taro dated February 12, 1997 (#8).] Taro then requested a meeting with the Agency and on June 4, 1997 Taro submitted an agenda and supporting information for a joint meeting with the Agency and SPHCP (Attachment #9).

On June 18, 1997, SPHCP and Taro had a joint pre-NDA meeting with the Division of Special Pathogens and Immunologic Drug Products (previously the Division of Anti-Infective Drug Products) and the Division of Over-the-Counter Drug Products. Agreements reached at that meeting included:

- It appeared reasonable to pool the two Schering clinical studies (93-34 and 93-40) as a single pivotal study

- FDA suggested that the pooled data be reanalyzed using the FDA's current evaluability criteria
- Pending the results of Taro's study (95-50), a determination will be made as to whether the pooled study from Schering can be used in conjunction with Taro's study to support approval of Schering's NDA
- FDA recommended that the two companies perform a "bridging" study demonstrating therapeutic equivalence between their respective formulations of the two percent products used for three days.

[Minutes of the meeting prepared by the Agency (#10) and SPHCP are attached. (#11)]

Details of the design of this "bridging" study were discussed in a telephone conversation with the medical reviewer, Joseph Winfield, M.D., on June 25, 1997. (See attached Schering telephone report - #12.) The protocol for the bridging study is included in Section 8.D. The study was initiated and more than two thirds of the patients are currently enrolled. It is expected that all patients will be entered by December 1, 1997, that the study will be complete in January 1998 and the results will be submitted as an amendment in February, 1998. This should allow sufficient time for an action letter within 6 months of this resubmission, as discussed at the June 18, 1997 meeting.

The Taro 3-day 2% vaginal cream used in the Taro clinical trial (#95-50) has been marketed by Taro in Canada as a prescription product for 7 years (1988-1995) and was switched to OTC status in 1995. Thus the product has been marketed for a total of nine years.

At the June 18, 1997 meeting there was discussion of whether Taro's safety data on a formulation essentially identical to the SPHCP 2% cream product could be used to support the marketing of the SPHCP formulation.

On September 29, 1997 a joint teleconference was held between SPHCP, Taro, the Division of OTC Drug Products and the Division of Special Pathogens and Immunologic Drug Products (DSPIDP) to discuss and reach agreement on this issue.

Prior to that teleconference, the rationale to support direct OTC marketing of SPHCP's 2% clotrimazole cream formulation for a 3 day treatment of vaginal yeast infections under an approved NDA was submitted to the Agency for its internal review and discussion. This information included safety data for both the active ingredient and the vehicle based on both companies' Rx and OTC marketing history of clotrimazole vaginal products,

as well as a formula comparison of SPHCP's and Taro's 1 and 2% clotrimazole creams. The information submitted and SPHCP's minutes of the teleconference are attached (#13). Detailed information on the Taro formulation, which was used in the Taro study #95-50 and is marketed in Canada, is included in this resubmission in the information provided on that clinical study.

Prior to the teleconference, the Agency had decided that the information was adequate to support the marketing of SPHCP's 2% clotrimazole cream formulation provided that the bridge study demonstrated therapeutic equivalency. This decision was then conveyed to the Sponsor during the teleconference.

Thus, NDA 20-574 requests approval to market the SPHCP 2% clotrimazole cream formulation for which detailed information is included in the original NDA with minor revisions included in this resubmission.

This resubmission includes the reanalysis of the results from the combined SPHCP studies, 93-34 and 93-40, using the criteria agreed upon at the April 3, 1996 meeting as well as all information required for Taro study 95-50. A reanalysis of the Taro data using the agreed upon criteria is also included. These studies comprise the two pivotal clinical trials which support the safety and efficacy of a 3-day 2% clotrimazole cream OTC therapy for vulvovaginal candidiasis. The results of these studies confirm that 3-day 2% clotrimazole cream treatment is equivalent to the currently approved 7-day 1% cream treatment and that clinical, mycological, and therapeutic cures of greater than 50% will occur following the use of either treatment regimen.

To assist in the review of this application, a disk containing the draft label text is provided in the medical reviewer's copy and a disk containing the statistical data for the Taro study (#95-50) is included in the statistical reviewers copy.

Patent information was included with the original NDA and has not changed. There are no unexpired U.S. Patents covering any aspect of this drug product or method of using the drug product.

In accordance with Section 306(k) of the FD&C Act, Schering-Plough HealthCare Products certifies that, with respect to this application, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306 (a) or (b) of the Act.

We further certify that the field copy has been sent to the FDA district office in San Juan, PR, which is the home district for the manufacturing site of this product in Manati, PR.

Should you have any questions regarding this application, please do not hesitate to contact me at (908) 604-1962.

Finally, please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331 (j).

Sincerely,



Ronald J. Garutti, M.D.
Vice President Clinical Research & Regulatory Affairs

Att.

Desk Copy: Christina Chi, Ph.D.
(cover letter and Summary Volume with Indices only)



NDA 20-574

Food and Drug Administration
Rockville MD 20857

Attention:
Ronald J. Garutti, M.D.
Vice President
Clinical Research & Regulatory Affairs
Schering-Plough Corporation
110 Allen Road
Liberty Corner, New Jersey, 07938-0276

DLG - 4 1997

Dear Dr. Garutti:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Gyne-Lotrimin 3™ 3-Day Vaginal Cream

Therapeutic Classification: Standard

Date of resubmitted Application: November 24, 1997

Date of receipt: November 25, 1997

Due date: November 25, 1998

Our Reference Number: NDA 20-574

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act in accordance with 21 CFR 314.101 (a).

If you have any questions, please contact:

Christina H. Chi, Ph.D.
Regulatory Health Manager,
(301) 827 - 2427

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Lisa Hubbard, R.Ph.
Acting Supervisor Project Management Staff
Division of Special Pathogens and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research



December 4, 1997

Schering-Plough Corporation
110 Allen Road
P.O. Box 278
Kenilworth, New Jersey 07033-0278
Telephone (908) 604-1640
Fax (908) 604-1540

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

PERSONAL DESK COPY

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
RESUBMISSION - NDA # 20-574
Additional Copies for Reviewers**

Dear Dr. Chi:

As requested, enclosed please find the following additional copies of specific sections of the subject resubmission for distribution to the reviewers:

Reviewer

Information

Linda Gosey
(Microbiology)

Microbiology Information: The cream product is tested according to the USP for the Microbial Limits Test and the Antimicrobial Preservatives Effectiveness test, as amended. The attached detailed analytical methods protocols (which are based on the USP methods) are for the reviewer's information only and includes the following: the Microbial Limits Test protocol used; the Antimicrobial Preservatives Effectiveness test protocol used; and the stability results.

Karen Lechter
(DDMAC - OTC)
Joann Spearmon
(DDMAC - DSPIDP)

Paper copy of the draft labeling with a disk (Word Perfect 6.0); and a copy of the cover letter for the Resubmission (no attachments).

**Gyne-Lotrimin 3™ 3-Day Vaginal Cream
RESUBMISSION - NDA # 20-574
Additional Copies for Reviewers**

Page 2

Reviewer

Information

Dr. Ling Chin
(OTC)

Dr. Linda Katz
(OTC)

Helen Cohran
(OTC)

Sakineh Walther
(OTC) (no disk)

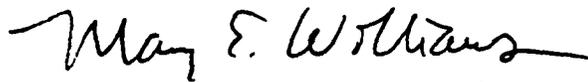
A copy of the Integrated Summary of Safety which includes Taro's marketing history; a copy of Taro's labeling for the product marketed in Canada; a paper copy of the draft labeling with a disk (Word Perfect 6.0); and a copy of the cover letter for the Resubmission (no attachments).

An extra copy of the label disk is provided for your convenience.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 604-1952.

Sincerely,



**Mary E. Williams
Associate Director Regulatory Affairs**

attachments



Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
P.O. Box 276
Kenilworth, New Jersey 07033-0276
Telephone (908) 604-1640
Fax (908) 604-1840

December 8, 1997

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

PERSONAL DESK COPY

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
RESUBMISSION - NDA # 20-574
Additional Copy for OTC Medical Reviewer**

Dear Dr. Chi:

As requested, enclosed please find the enclosed additional copy of Section 8. for the OTC Division medical reviewer.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs

attachments

12/9/97
Received LC
4 volumes



Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 604-1840

December 15, 1997

Joseph Winfield, M.D.
Medical Review Officer
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

PERSONAL DESK COPY

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574 - AMENDMENT
Patient Data Listings for Protocols #93-34 and #93-40**

Dear Dr. Winfield:

Enclosed please find the Patient Data Listings for Protocols #93-34 and #93-40 as requested. If you need any additional information, please don't hesitate to contact me at (908) 604-1952.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs

Desk copy: Dr. Christina Chi (cover letter)



Schering-Plough
HealthCare Products

December 15, 1997

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574 - AMENDMENT
Patient Data Listings for Protocols #93-34 and #93-40**

Dear Dr. Goldberger:

At the request of your Medical Review Officer, Dr. Joseph Winfield, we are herein providing copies of the patient data listings for protocols #93-34 and #93-40 which have been reanalyzed using the FDA's current evaluability criteria.

Patient data listings had been previously submitted with the original application (4/27/95) using the established criteria at that time. However, at our April 3, 1996 meeting with the FDA, the evaluability criteria were redefined and subsequently applied to the subject studies. Information on the reanalysis of the data was provided in Vol. 2.1, Section H. of our Resubmission on November 24, 1997, but did not include the patient data listings.

Should you have any questions regarding this information, please don't hesitate to contact me at (908) 604-1962.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Ronald J. Garutti, M.D.
Vice President Clinical Research & Regulatory Affairs

duplicate

Desk copy: Dr. J. Winfield (complete), Dr. C. Chi (cover letter)



Schering-Plough
HealthCare Products

December 16, 1997

Schering-Plough Corporation
1515 North 17th Street
Kenilworth, NJ 07033
Tel: 908-646-2000
Fax: 908-646-2000

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574
REQUEST FOR TELECONFERENCE**

Dear Dr. Goldberger:

On December 11, 1997, we received notice of FDA's receipt of the subject NDA resubmission. Included in this notification was a "Due date" of November 25, 1998, which established a review clock of one year. This timing greatly exceeded our expectations of a six month review period.

Therefore, as discussed with your Dr. Christina Chi yesterday, we are requesting a teleconference, at the earliest time possible, between the appropriate Divisions at the FDA and Schering-Plough HealthCare Products/ Taro for discussion and clarification of the review clock.

Prior to the teleconference we will submit a detailed discussion of our position on this matter. Please don't hesitate to contact me at (908) 604-1962 if you have any questions regarding this request.

Sincerely,

Ronald J. Garutti, M.D.
Vice President Clinical Research & Regulatory Affairs

copy: Dr. C. Chi

N.C.



December 18, 1997

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologic Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574 - CORRESPONDENCE**

Dear Dr. Goldberger:

On December 15, 1997, at the request of your Medical Review Officer, Dr. Joseph Winfield, we provided additional copies of the patient data listings for protocols #93-34 and #93-40 which had been reanalyzed using the FDA's current evaluability criteria. This information had been previously provided in the November 24, 1997, Resubmission of the subject NDA in Vol. 2.2, Section 8.G. Integrated Summary of Efficacy (Table 3, pages 175 to 192).

If you have any additional questions or concerns, please don't hesitate to contact me at (908) 604-1962.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ronald J. Garutti' with a stylized flourish at the end.

Ronald J. Garutti, M.D.
Vice President
Clinical Research / Regulatory Affairs

duplicate
Desk copy: Dr. J. Winfield, Dr. J. Chi



January 8, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE
BRIDGE STUDY REPORT (PROTOCOL CTZ-9701)**

Dear Dr. Goldberger:

We are herein providing the final report of the bridge study (Protocol CTZ-9701) which demonstrates the therapeutic equivalence of the Taro Pharmaceuticals' and the Schering-Plough HealthCare Products' (SPHCP) 2% clotrimazole vaginal cream formulations.

This bridge study had been recommended by the FDA at the June 18, 1997 pre-NDA meeting between Taro, SPHCP, the Division of Special Pathogens and Immunologic Drug Products (DSPIDP), and the Division of Over-the-Counter Drug Products (OTC), as a means to demonstrate the therapeutic equivalence of the two formulations used in the NDA clinical studies. In our November 24, 1997 Resubmission of the subject NDA, we informed you that the bridge study was near completion and the results would be submitted as an amendment in February, 1998.

However, given the priority of this application for both companies, the analysis of the results was expedited and we were able to exceed the projected timing of completion. We are therefore enclosing the final study report and key tables for the subject bridge study. Please note: while the clinical study report is final, it is being submitted unofficially at this time to facilitate your 45-day review for acceptability to file. The final document with all appropriate information and data formatted according to your guideline on Format & Content of Clinical and Statistical Sections of an NDA will be formally submitted as an Amendment to this application within the week.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you have any questions regarding this matter, please don't hesitate to contact me at (908) 604-1962.

Sincerely,



Ronald J. Garutti, M.D.
Vice President Clinical Research & Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

Attachments

Desk Copy: Christina Chi, Ph.D. (4 complete copies)

mw



Schering Plough
HealthCare Products

^{B2}
~~ORIG-AMENDMENT~~

ORIGINAL

3115
110
P.O.
Liberty
Telephone
Fax

January 15, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV
HFD-590;
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852



Subject: **AMENDMENT: BRIDGE STUDY CTZ 97-01**
NDA 20-574: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
(2% clotrimazole)

Dr. Goldberger:

Schering-Plough HealthCare Products (SPHCP) is herein submitting an Amendment to New Drug Application (NDA) 20-574 which was resubmitted on November 24, 1997.

This Amendment contains the **complete study report of the bridging study (#CTZ-97-01)** which determined the therapeutic equivalence between the SPHCP and Taro Pharmaceuticals U.S.A., Inc. 2% clotrimazole vaginal cream formulations.

This bridging study was recommended by the Agency in order to allow the clinical trial conducted on the Taro vaginal cream formulation to be used as the second pivotal efficacy trial for approval of the SPHCP formulation which is the subject of this NDA #20-574.

The results of this bridging study demonstrate the therapeutic equivalence of the two formulations and indicate that use of the products result in significant mycological, clinical and therapeutic cures which exceed the 50% requirement for over-the-counter approval. A data disk is provided in Volume 2, 10.D. Database User Guide.

In accordance with Section 306(k) of the FD&C Act, Schering-Plough HealthCare Products, Inc. certifies that, with respect to this amendment, it did not knowingly use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

8. CLINICAL DATA

A. List of Investigators

B. Background/Over-view of Clinical Investigations

Protocol CTZ 97-01

Tables

Mark Goldberger, M.D., Director

Page 2

January 15, 1998

Should you have any questions regarding this amendment or the NDA, please do not hesitate to contact me at (908) 604-1962.

Please be advised that the information in this amendment is confidential. The legal protection of such confidential material is hereby claimed under applicable provisions in 18 U.S.C., Section 1905 or 21 U.S.C., Section 331 (j).

Sincerely,



Ronald J. Garutti, M.D.

Vice President,

Clinical Research/Regulatory Affairs

Desk copy: Christina Chi, Ph.D. (4 copies)

Clinical Investigations

Protocol CTZ 97-01



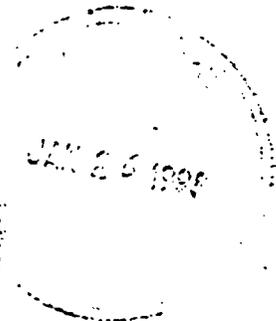
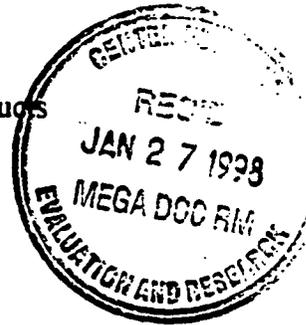
NC

NEW CORRESP
ORIGINAL

Drug Evaluation
and Research Products

January 23, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852



**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Goldberger:

On January 12, 1998, Dr. Christina Chi (FDA Project Manager) requested additional copies of information previously submitted to this application for distribution to reviewers. The requested information is being provided as follows:

- 3 desk copies of the Statistical Section (Vol. 1.28 to 1.44) from the original application (submitted 4/27/95) with SAS Data disks are being sent to Dr. Chi. These copies are identical to the original application except for the Database User's Guide and disk which have been updated to include the new criteria established by the FDA. This information was requested by Dr. Aloka Chakravarty (FDA Biometric Reviewer) on January 13, 1998.
- We were informed that the SAS Data Disk for Taro's study (# 95-50) contained a file that was "unreadable." Therefore 2 new copies of the entire disk are being sent to the Central Document Control Room (see attached) for the archive and review copies of the November 24, 1997 Resubmission. An additional two desk copies are being concurrently sent to Dr. Chi for distribution to reviewers.

An additional copy of the proposed labeling and disk (Word Perfect 6.0) is being sent to Dr. Chi for the microbiologist reviewer.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

We believe this information satisfies all of Dr. Chi's requests. Please don't hesitate to contact me at (908) 604-1962 if you need anything further.

Sincerely,

A handwritten signature in black ink that reads "Ronald J. Garutti" with a stylized flourish at the end.

Ronald J. Garutti, M.D.

Vice President Clinical Research & Regulatory Affairs

Attachments

Desk Copy: Christina Chi, Ph.D.



Schering-Plough
HealthCare Products

January 28, 1998

Schering-Plough Corporation
110 Allen Road
P.O. Box 275
Kenilworth, New Jersey 07033-0275
Tel: (908) 604-1640
Fax: (908) 604-1547

PERSONAL DESK COPY

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Chi:

Please find the enclosed desk copy of the January 12, 1998 teleconference minutes, concurrently submitted to the Central Document Control Room, which pertain to the review clock for the resubmission of the subject NDA.

In return, we request that you provide us with a copy of your minutes as soon as they become available per MaPP 4512.1.

If you have any questions or concerns regarding SPHCP's minutes, don't hesitate to contact me at (908) 604-1952.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Mary Williams
Associate Director Regulatory Affairs



January 28, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852



**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Goldberger:

Please find the enclosed copy of our minutes for the teleconference held January 12, 1998, between members of your Division and Schering-Plough HealthCare Products (SPHCP), to discuss the one-year review clock assigned to the resubmission of the subject NDA. In return, we request that you provide us with a copy of your minutes as soon as they become available per MaPP 4512.1.

If you have any questions or concerns regarding SPHCP's minutes, don't hesitate to contact me at (908) 604-1962.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Ronald J. Garutti, M.D.
Vice President Clinical Research & Regulatory Affairs

mw

Desk copy: Dr. Christina Chi



Schering-Plough
HealthCare Products

January 30, 1998

Schering-Plough Corporation
119 Avenue Road
Kenilworth, NJ 07033
United States of America
Telephone (908) 271-4000

PERSONAL DESK COPY

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Chi:

Please find the enclosed desk copy of a recent amendment to the subject NDA regarding changes to the control operations sites.

If you have any questions regarding this matter please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs



January 30, 1998

Stamp date:

CDER: Feb. 2, 1998.

Meq. doc. rev. Feb. 3, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologic Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: AMENDMENT**

Dear Dr. Goldberger:

Changes have been made to the sites of control operations for the subject product. Please find the enclosed "Sites of Manufacture, Packaging, and Controls Operations" page which has been revised and replaces that contained in our November 24, 1997 Resubmission of the subject NDA.

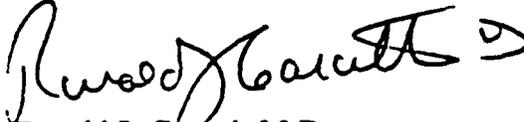
The changes to the control operations sites include the deletion of our facility in Union, NJ, for business reasons. In addition, our facility in Cleveland, TN, has been added as a site for Microbial Limits testing. (Note: the operations for the Microbiological Control Laboratory had been transferred from our Memphis TN, facility to our Cleveland TN, facility in August 1997.)

The change in the control operations sites has been discussed with the FDA Chemistry Reviewer, Dr. Dorota Matecka, and the attached page is being concurrently submitted to her via facsimile. We further certify that the field copy is being concurrently submitted to the FDA district office in San Juan, PR, which is the home district for the manufacturing site of this product in Manati, PR.

If you have any questions or concerns regarding this information, please don't hesitate to contact me at (908) 604-1962.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,



Ronald J. Garutti, M.D.

Vice President Clinical Research & Regulatory Affairs

mw

2 copies: archive and review

Desk copy: Dr. Christina Chi



March 17, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

**RESPONSE TO REQUEST
FOR INFORMATION**

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Goldberger:

Schering-Plough HealthCare Products (SPHCP) is herein providing additional foreign safety information to support direct over-the-counter (OTC) marketing of the pending subject application, as requested by the FDA in a January 12, 1998 teleconference.

Background

FDA informed SPHCP and Taro in a September 29, 1997 teleconference that the OTC Division and DSPIDP agreed the information submitted previously by the sponsors (i.e., comparison of their 1% and 2% clotrimazole vaginal cream formulas and their marketing history (see Vol.2.1, pages 060- 063, 11/25/97 submission)), should be adequate to support the use of SPHCP's 2% clotrimazole vaginal cream formulation for direct OTC marketing, provided that the results of a bridge study demonstrated therapeutic equivalency. To further support this decision, FDA requested that Taro's safety data for their marketed 2% product in Canada be provided to the subject NDA.

Subsequently, information on Taro's safety data was provided in the November 25, 1997 reactivation of the subject NDA (Integrated Summary of Safety, Vol. 2.2 page 216). However, since the information was limited to "no serious adverse events reported," the FDA requested further explanation of the product's use history (Rx and OTC).

Additional Foreign Safety Information

The Taro 2% clotrimazole vaginal cream formula was marketed as a prescription product in Canada from 1989 until 1995, when it was switched to its current OTC status. Since it was first marketed in 1989, Taro has sold approximately [redacted] tubes of this product and has not received any adverse event reports (ADR). See attached letter from Dr. Moros (Taro) to Dr. Garutti (SPHCP).

This is consistent with SPHCP's own low incidence of reported adverse events for clotrimazole. An estimated [redacted] have been sold since 1978 with only 418 non-serious adverse events and 2 serious adverse events reported (see Vol. 2.2 page 216 of the November 25, 1997 NDA Resubmission for details of the serious adverse event reports). [redacted]

To further assist your consideration of Taro's foreign safety data, we are attaching a correspondence from Taro which includes information on all reported complaints from November 1989 to December 1997 for *all* of their clotrimazole cream products (i.e, vaginal and topical) sold in the U.S. and Canada. There are a total of 22 product complaints, of which only 4 qualify as an adverse event. In addition, we are also enclosing a copy of Taro's SOP for tracking product complaints for your information.

We trust this information, in concert with the long history of safe use of clotrimazole in the marketplace, is adequate to satisfy any concerns you may have regarding direct OTC marketing of the SPHCP clotrimazole 2% vaginal cream product. If we can be of further assistance, please don't hesitate to contact me at (908) 604-1962.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

May E. Williams / for

Ronald J. Garutti, M.D.
Vice President Clinical Research/ Regulatory Affairs

mw
attachment; desk copy to Dr. C. Chi



March 24, 1998

Mark Goldberger, M.D., Director
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

4 MONTH SAFETY UPDATE REPORT

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: AMENDMENT**

Dear Dr. Goldberger:

The enclosed safety update report is being submitted to the pending subject application as required under 21 CFR 314.50(d)(5)(vi)(b).

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

Ronald J. Garutti, M.D.
Vice President, Clinical Research/Regulatory Affairs

mw
attachment/ duplicate
Desk copy (Dr. Christina Chi

NDA 20-574: Gyne-Lotrimin 3™ 3-Day Cream

4 MONTH SAFETY UPDATE

Per 21 CFR 314.50(d)(5)(vi)(b), we are herein updating our pending application with the following safety information learned since the date of the NDA reactivation (11/24/97).

Bridge Study

The results of a bridge study to determine the therapeutic equivalence between the Schering Plough HealthCare Products (SPHCP) and Taro Pharmaceutical USA, Inc. 2% clotrimazole cream formulations were previously submitted in an Amendment to the NDA on January 15, 1998. Out of 147 patients randomized to the 2 treatment groups, 1 patient was reported to have an adverse event which the investigators considered to be remotely related to the study drug (see attached). There were no serious drug-related adverse events reported and no patient discontinued the study drug due to an adverse/ clinical event.

Post Marketing Adverse Events (ADEs) Reported to the Sponsors

Taro Pharmaceuticals markets clotrimazole vaginal cream in 1% and 2% formulations in Canada and in a 1% formulation in the United States. The information on Taro's safety data provided in the reactivation of the subject NDA was limited to "no serious adverse events reported." At the request of the FDA for further explanation, correspondence was submitted to the NDA on March 17, 1998, regarding Taro's marketing history and their method of tracking consumer complaints. There are no new serious adverse events reported for these products in the United States or Canada since the date of the NDA reactivation.

SPHCP markets clotrimazole vaginal cream in a 1% formulation in the United States. There are no new serious adverse events reported for this product since the date of the NDA reactivation.

Medical Literature Reports of Adverse Events for 3-day Clotrimazole Therapy

A review of the medical literature revealed no new information on clinical studies published since the time of our submission.

Other Information

There have been no new reports of animal drug studies being conducted with clotrimazole.

There have been no reports to the Sponsor of any drug interactions with clotrimazole vaginal cream therapy.



April 16, 1998

Stella Machado, Ph.D.
Statistics Reviewer
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
Food and Drug Administration
198 Grange Loan
Edinboro, Scotland UK EH9 2DZ

STATISTICAL INFORMATION

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Machado:

As discussed in the April 1, 1998, telephone conversation between FDA and Schering-Plough HealthCare Products (SPHCP), the following information is being provided in response to your requests:

SPHCP - Protocols 93-34 and 93-40

Issue: You have not received the data disks for the Schering-Plough studies.

*Response: The SAS data disks for the Schering-Plough studies were submitted with the original application on April 27, 1995. At FDA's request in a January 12, 1998 teleconference, the SAS data disks were sent again on January 23, 1998, with 3 additional desk copies of the Statistical Section (Vol. 1.28 to 1.44) from the original application. Following our conversation on April 1st, Dr. Chi called back to inform me that these data disks had been located and would be given to you before you departed. If you still have *not* received these disks, please notify us immediately and we will send them directly to you.*

Taro - Protocol 95-50

Issue: You have received the reformatted SAS data disks (sent to FDA on March 5, 1998) and are able to retrieve the data using the SAS transportable file provided; however, you cannot find the "labs.sd2" file.

Response: The original disk prepared by Taro had listed a "labs.sd2" file. However, this was an empty data set which had been saved to the disk by mistake and was not included in the reformatted version prepared by SPHCP's statistician. All of the laboratory data is contained on the reformatted disk in the "labdata.sd2" file and can be recovered when the 9550.exe file is expanded.

Taro - Bridge Study Protocol CTZ 97-01

Issue: You have received the reformatted SAS data disks (sent to FDA on March 5, 1998) and are able to retrieve the data using the SAS transportable file provided; however, you cannot find the "alldat.sd2" and "calls.sd2" files.

Response: The original disk prepared by Taro contained an "alldat.sd2" file which was a compilation of all the information contained in the other data sets. When SPHCP's statistician reformatted the SAS data disks, this file was not included since the information was contained in other files on the disk and would have been redundant.

The original disk prepared by Taro also contained a "calls.sd2" file. Unfortunately this file was not included in the information sent to SPHCP's statistician and therefore was not included in the reformatted SAS data disks sent to the FDA. This file is being provided now on the enclosed SAS data disk. We apologize for the inconvenience.

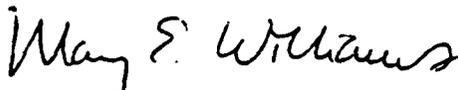
Issue: Requested the SAS programming code used to calculate the summary variables in the data analysis.

Response: The SAS programming code used to calculate the summary variables in the data analysis is provided on the following page.

We trust this information satisfies all of your requests. If you require any additional information please don't hesitate to contact me at (908) 604-1952.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,



Mary E. Williams
Associate Director Regulatory Affairs

mw
attachment, disk
Desk copy: Dr. C. Chi



Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 604-1840

May 1, 1998

Christina H. Chi, Ph.D.
Project Manager
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

PERSONAL DESK COPY

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Dr. Chi:

Enclosed, please find an additional desk copy of Volume 2.3 of the November 24, 1997 Resubmission as requested. Note: this volume contains the revised labeling submitted as an amendment to the subject NDA on February 24, 1998, which deleted an indication for relief of external vulvar itching and irritation associated with a yeast infection.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If you require any additional information, please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs



Schering-Plough
HealthCare Products

May 12, 1998

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 604-1840

Linda Gosey, Microbiologist
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20857

PERSONAL DESK COPY

**SUBJECT: Gyne-Lotrimin 3™ 3-Day Vaginal Cream
NDA # 20-574: CORRESPONDENCE**

Dear Ms. Gosey:

Per your request for information on the species identified for positive cultures at Visits 2 and/or 3, Schering-Plough HealthCare Products (SPHCP) is herein enclosing an additional copy of the following information previously submitted to this new drug application for your review:

<u>PROTOCOL</u>	<u>DATE</u>	<u>VOLUME</u>	<u>PAGES</u>
# 93-34 (SPHCP)	Original 4/27/95	1.20	08 2836 to 08 2935
# 93-40 (SPHCP)	Original 4/27/95	1.26	08 4622 to 08 4691
# 95-50 (Taro)	Resubmission 11/24/97	2.9	244 to 273

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

If we can be of further assistance, please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams
Associate Director Regulatory Affairs

Desk Copy: Dr. Chi (cover letter only)

5/13/98 { Christina received & forwarded one packet & letter in Dr. Gosey's mailbox.