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 19, 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

REQUEST FOR MEETING

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

Dear Dr. Goldberger:

The sponsors of the subject new drug application, Schering-Plough HealthCare Products (SPHCP) and Taro Pharmaceuticals Inc., formally request a meeting with the appropriate FDA divisions to discuss the proposed labeling for the Gyne-Lotrimin 3™ 3-Day Vaginal Cream product, submitted with the November 24, 1997, reactivation of the subject NDA and amended on February 24, 1998.

SPHCP is aware that proposed class labeling for vaginal antifungal products is scheduled for discussion in a July Advisory Committee meeting. However, we wish to meet with the Agency as soon as possible, either before the Advisory Committee meeting, or if need be, immediately thereafter. From a commercial standpoint, the lead time to develop packaging components can be lengthy (up to 16 weeks for a tube), making the timing of the labeling approval critical to the success of the product launch.

The specific objective(s)/outcome(s) the sponsor expects from the meeting:

- Subject to approval of the pending NDA, the sponsors seek approval from all of the appropriate FDA divisions on the proposed labeling.

The proposed agenda for this meeting:

- Sponsors to present overview of each labeling component (i.e., carton, tube, and educational pamphlet) and the rationale for the contents and format — 15 minutes
- Discussion — 35 minutes

Planned Sponsor attendees:

- Ronald Garutti, M.D., Vice President, Clinical Research/Regulatory Affairs, SPHCP
- Daniel Moros, M.D. Vice Chairman, Taro Pharmaceuticals U.S.A., Inc., Taro
- Mary Williams, Associate Director Regulatory Affairs, SPHCP

Requested participants from the Agency:

- Appropriate representatives from the Division of Special Pathogens and Immunologic Drug Products (DSPIDP)
- Appropriate representatives from the Division of Over-the-Counter Drug Products (DODP)
- Appropriate representatives from the Division of Drug Marketing, Advertising and Communications (DDMAC)

Supporting documentation will be submitted to the Agency at least two weeks prior to the scheduled date of the meeting.

Please be advised that this information and any subsequent submission and meeting are 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).

Thank you in advance for your consideration in arranging this meeting. If you have any questions, please don't hesitate to contact me at (908) 604-1962.

Sincerely,

Mary E. Williams /for

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

Desk copy: Dr. Debra Bowen (DODP), Dr. Christina Chi (DSPIDP)

Arrived at C Chi's desk: JUN 12 1998

Schering-Plough
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June 11, 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:

At the request of Dr. Winfield, we are submitting an amendment to NDA 20-574 which provides detailed information on the reconciliation of the evaluable patient populations in the original analysis and those in the re-analysis. Enclosed are desk copies of this amendment for you and Dr. Winfield. Please give Dr. Winfield his copy as soon as possible to minimize the loss of review time.

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).

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

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

attachment

June 11, 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

Additional Clinical Study Tables

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

Dear Dr. Goldberger:

Enclosed, as requested by Dr. Joseph Winfield, is a reconciliation of the evaluable patient populations in the original analysis of clinical studies 93-34 and 93-40 and in the re-analysis of these studies (Attachment I). Additional detailed information on the disposition of the patients and the reasons for exclusion are provided in Attachment II as follows:

Tables 1a and 1b	Disposition of Patients in Re-analysis of Studies 93-34 and 93-40
Table 2	Reasons for Exclusion from Re-analysis (totals)
Table 3	Patients Excluded from Re-analysis

The 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 there are any additional questions, please don't hesitate to contact me at (908)604-1962.

Sincerely,

Mary E. Williams / for

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

Desk copy: Dr. J. Winfield (Medical Reviewer), Dr. Christina Chi (Project Manager)

NDA 20-574

JUN 12 1998

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

Dear Dr. Garutti:

We acknowledge receipt on May 20, 1998, of your May 19, 1998, correspondence requesting a meeting to discuss the proposed labeling for the Gyne-Lotrimin 3 ™ 3-Day Vaginal Cream. We have concluded that the meeting is premature because our review will not be sufficiently complete to justify a labeling meeting.

If you disagree that a meeting is not necessary at this time, we encourage you to discuss the matter with Christina H. Chi, Ph.D., Project Manager, of this division. If the issue cannot be resolved at the division level, you may submit an appeal to James C. Morrison, Ombudsman for the Center for Drug Evaluation and Research (301-594-5443). A copy of any appeal should be sent to the Division of Special Pathogen and Immunologic Drug Products (HFD-590).

If you have any questions, contact: Christina H. Chi, Ph.D.,
Project Manager,
at (301) 827-2349

Sincerely yours,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and
Immunologic Drug Products (DSPIDP)
HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/S/

Debra Bowen, M.D.
Director
Division of Over-the-Counter Drug
Products (DOTCDP)
HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research

6/12/98

Schering-Plough
HealthCare Products

Schering-Plough Corporation
[illegible]
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June 23, 1998

Linda Utrup, Ph.D.
Microbiologist
Office of Drug Evaluation IV
Div. of Special Pathogens and Immunologics Drug Products
HFD-590, Room N352
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. Utrup:

At the request of Dr. Christina Chi, we are providing additional copies of the following volumes which were previously submitted to the subject NDA:

VOLUME	CONTENT	SUBMITTED
Vol. 1.20	8. Clinical Data Section - Protocol 93-34	4/27/95
Vol. 1.26	8. Clinical Data Section - Protocol 93-40	4/27/95
Vol. 2.4	8. Clinical Data Section - Protocol 95-50	11/24/97
Vol. 2.7	10. Statistical Section - Protocol 95-50	11/24/97
Vol. 2.8	10. Statistical Section - Protocol 95-50	11/24/97
Vol. 2.9	10. Statistical Section - Protocol 95-50	11/24/97

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 on this information, please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

enclosure; desk copy - Dr. C. Chi

DUPLICATE

Schering-Plough
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July 30, 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

REQUEST FOR MEETING

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: LABELING

Dear Dr. Goldberger:

On May 19, 1998, the sponsors of the subject new drug application, Schering-Plough HealthCare Products (SPHCP) and Taro Pharmaceuticals Inc., formally requested a meeting with the appropriate FDA divisions to discuss the proposed labeling for the Gyne-Lotrimin 3® 3-Day Vaginal Cream product. However, the Agency concluded that the request was premature because the review of the NDA submitted on November 24, 1997, would not be sufficiently advanced to justify a meeting at that time.

We have since been advised by Dr. Christina Chi that the appropriate FDA divisions should be ready to meet with us on this issue mid-September (tentative dates: September 16 or 17, 1998). Therefore, we are hereby formally requesting a meeting to discuss the proposed labeling for the subject product at the earliest possible date.

The specific objective(s)/outcome(s) the sponsor expects from the meeting:

- Subject to approval of the pending NDA, the sponsors seek approval from all of the appropriate FDA divisions on the proposed labeling.

The proposed agenda for this meeting:

• Sponsors to present overview of each labeling component (i.e., carton, tube, and educational pamphlet) and the rationale for the contents and format	30 minutes
• Discussion	90 minutes

Planned Sponsor attendees:

- Ronald Garutti, M.D., Vice President, Clinical Research/Regulatory Affairs, SPHCP
- Mary Williams, Associate Director Regulatory Affairs, SPHCP

Requested participants from the Agency:

- Appropriate representatives from the Division of Special Pathogens and Immunologic Drug Products (DSPIDP)
- Appropriate representatives from the Division of Over-the-Counter Drug Products (DODP)
- Appropriate representatives from the Division of Drug Marketing, Advertising and Communications (DDMAC)

Supporting documentation, if any, will be submitted to the Agency at least two weeks prior to the scheduled date of the meeting. Please note: SPHCP is in the process of revising the labeling for the carton and educational pamphlet at Dr. Brad Leissa's recommendation to model our labeling after the most recently approved product for vaginal yeast - Monistat 3-day Cream. The revised labeling will be submitted in an amendment to this NDA as soon as it is available.

Please be advised that this information and any subsequent submission and meeting are 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).

Thank you in advance for your consideration in arranging this meeting. If you have any questions, please don't hesitate to contact me at (908) 604-1962.

Sincerely,

Mary E Williams / for

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

Desk copy: Dr. Debra Bowen (DODP), Dr. Christina Chi (DSPIDP)

Schering-Plough
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August 3, 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: LABELING - COLORED COPIES

Dear Dr. Chi:

Enclosed, please find colored mock-up labeling (20 copies) for the subject product as requested. In addition, copies of this colored mock-up labeling are being concurrently sent to Karen Lechter and Joanne Spearmon in the Division of Drug Marketing, Advertising and Communications for their review.

The labeling for this product has been revised again based on Dr. Brad Leissa's recommendation to model our labeling after the most recently approved product for vaginal yeast - Monistat 3-day Cream. Additional changes were also made to incorporate recent revisions requested by the OTC Division for our Gyne-Lotrimin 7-day Cream. I will submit the labeling in text format with a corresponding disk (WordPerfect 6.0) as soon as it is available.

Thank you for your assistance in this matter. If you have any questions please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

attachments

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August 7, 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: AMENDMENT

Dear Dr. Chi:

Enclosed, please find your desk copy of the amendment being concurrently submitted to the subject NDA regarding microbiology information. This information was also sent via facsimile to you and Ms. Patricia Hughes earlier today.

Finally, I wanted to inform you that copies of the colored mock-up labeling were also sent to Mr. Robert Eshelman and Mr. William Nychis in the Office of Compliance as requested.

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 please don't hesitate to contact me at (908) 604-1952.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

attachments

BI

DRUG AMENDMENT

ORIGINAL

Schering-Plough HealthCare Products

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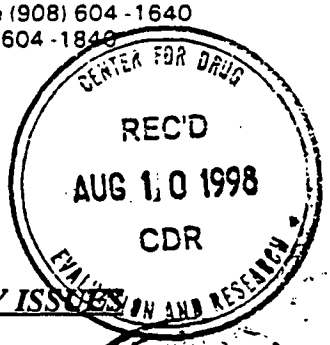
August 7, 1998



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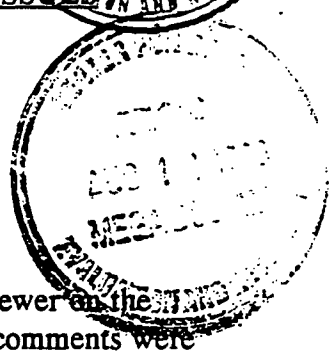
Central Document Control Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

MICROBIOLOGY ISSUES



SUBJECT: NDA # 20-574, Gyne-Lotrimin 3® 3-Day Vaginal Cream AMENDMENT

Dear Dr. Goldberger:

On July 22, 1998, we received a list of comments from the microbiologist reviewer on the Antimicrobial Preservative Effectiveness Test data for the subject NDA. The comments were discussed in a teleconference on July 27, 1998 with Ms. Patricia Hughes (FDA microbiologist), Mr. Stephen Richards (Schering Laboratories microbiologist) and Ms. Mary Williams (SPHCP Regulatory Affairs). For your convenience, each comment is listed below in italics and followed by SPHCP's response.

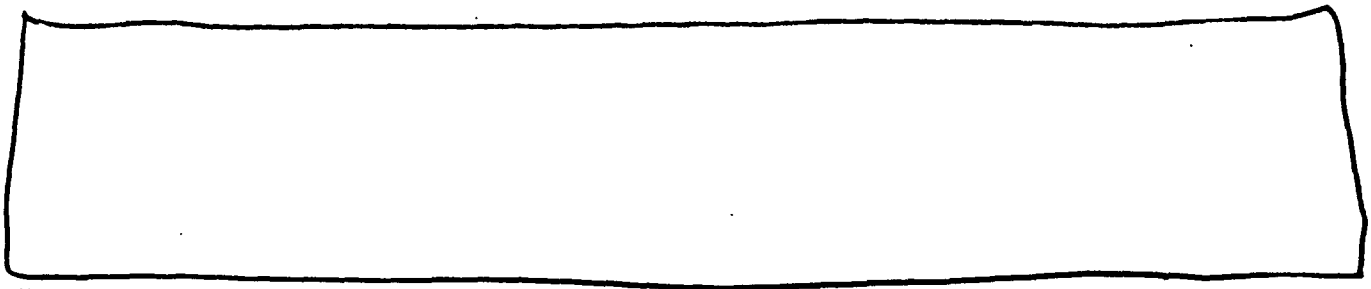
1) *Please submit the Antimicrobial Preservative Effectiveness Test protocol used for this drug product. In general, the microbial count data does not appear to be very reproducible. Was the product adequately sampled?*

A copy of the APE protocol used for these studies, as well as a copy of the current APE protocol which has been modified to comply with the USP 23, 8th Supplement (effective May 15, 1998) is enclosed.

[redacted]

2) *The APET test criteria were not met for E. coli in Batch No. 92165 three month stability sample at* [redacted] *This result may be spurious. Please provide justification or explanation.*

This portion of the document contains information that will not be included in the redacted portion of the document for the public to obtain.



Following the above discussion, SPHCP agreed to submit up to 24 months of stability data on an additional batch which had been manufactured in September 1995. (See attached report.) Please note: because the NDA was withdrawn in January 1996, and the stability study was placed on hold, tests were not conducted at all of the time points listed in the stability protocol. Therefore, results of the APE tests at the initial and 3 month time intervals are included in the attached stability report, and an additional APE test is currently being conducted at a 31 month interval. This data will be submitted as soon as it becomes available. Please note: A field copy of this amendment 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. A copy of the field copy certification is enclosed.

Also as agreed in the teleconference, SPHCP committs to conduct APE testing on the first marketed production batch of this product and provide the results to the FDA post NDA approval. In addition, SPHCP committs to include selective media for yeast and mold recovery as part of the Microbial Limits Test for the production batches of this product.

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 trust this information satisfies all of your concerns regarding this matter. Please do not hesitate to contact me at (908) 604-1962 if you require any additional information.

Sincerely,

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

Desk Copy: Dr. Christina Chi

BL

ORIG AMENDMENT

ORIGINAL

Schering-Plough
HealthCare Products

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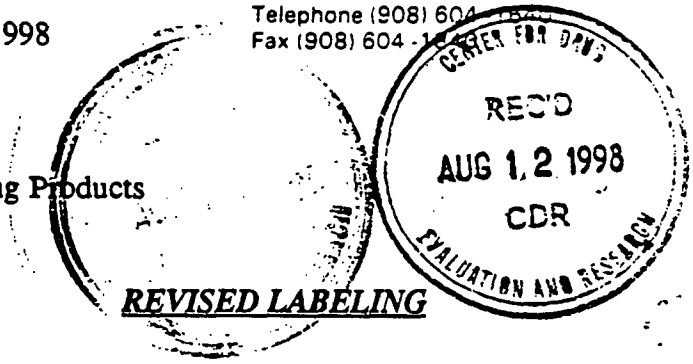
August 11, 1998



REVISED LABELING

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

Dear Dr. Goldberger:

We are herein providing the revised labeling (and corresponding disk in Word Perfect 6.0) for the subject NDA as promised in our July 30, 1998, correspondence which requested a meeting to discuss the labeling with the appropriate Agency divisions prior to approval of the NDA. Identical colored mock-up labeling was submitted to Dr. Christina Chi and several reviewers on August 3,1998. Please note: the revisions to this labeling were made based on Dr. Brad Leissa's recommendation to model the carton and educational pamphlet after the recently approved label for Monistat 3-day Cream, as well as additional changes recommended by the OTC Division for the Gyne-Lotrimin 7-day Cream label in a July 15, 1998 teleconference. We trust this revised labeling is satisfactory and look forward to discussing it with you at the meeting tentatively scheduled for September 17, 1998.

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/for

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

attachments
Desk Copy: Dr. C. Chi, Ms. Cheryl Turner

bc

Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
PO Box 276
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August 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 FDA QUESTIONS

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: CMC AMENDMENT

Dear Dr. Goldberger:

Schering-Plough HealthCare Products (SPHCP) received Dr. Dorota Matecka's (FDA Chemistry Reviewer) comments on the Chemistry, Manufacturing, and Controls (CMC) information for the subject NDA in a July 14, 1998, facsimile. For your convenience these comments are listed below in italics, followed by our response.

1. *Please describe the in-process controls for the manufacturing process of the drug product. For bulk product testing, samples should be taken not only from the top, but also from the middle and bottom of the compounder.*

2. *Please include a viscosity specification for the drug product. Viscosity should also be monitored on stability.*

In response to this request, SPHCP has developed an analytical method to measure the viscosity of the subject clotrimazole cream, 2%, and is herein enclosing a copy of this test method in Attachment 1. However, there is

This portion of the document contains information that will not be included in the redacted portion of the document for the public to obtain.

ORIG NEW CORRES

ORIGINAL

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ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

Addendum

August 26, 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

ADDITIONAL INFORMATION ON MARKETING HISTORY

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

Dear Dr. Goldberger:

In response to a telephone request made by Dr. Ling Chin (Division of OTC Drug Products) on August 20, 1998, we are herein submitting additional information to the subject NDA on the marketing history of clotrimazole vaginal cream products. Much of this information was recently provided in support of Schering-Plough HealthCare Products' (SPHCP) request for direct OTC marketing of a potential 1-day clotrimazole cream (4%) product under IND [redacted] (subject of a DSPIDP/ OTC / SPHCP meeting on August 3, 1998).

The information contained in the following pages consists of:

(1) Available worldwide marketing information on vaginal clotrimazole cream products

(2) A summary of SPHCP adverse event reports associated with the intravaginal use of clotrimazole vaginal cream 1% for the last ten years (1988-1997).

(3) Available adverse event reports on the 10% clotrimazole vaginal cream product marketed in Canada

(4) Adverse event reports associated with the intravaginal use of clotrimazole as reported by the World Health Organization Drug Monitoring Programme (WHO)

We trust this information provides further support for the safety of direct OTC marketing of the clotrimazole vaginal cream 2% product for the subject NDA.

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 /for

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

attachments
Desk Copy: Dr. C. Chi, Dr. Ling Chin

ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

Addendum

Schering-Plough
HealthCare Products

Schering-Plough Corporation
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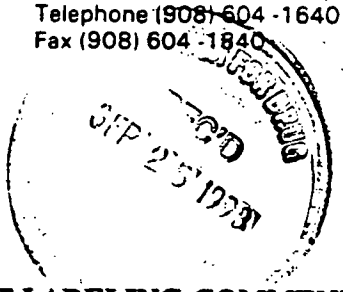
September 24, 1998



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

DRAFT LABELING COMMENTS

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: GENERAL CORRESPONDENCE

Dear Dr. Goldberger:

This is in response to a September 10, 1998, facsimile from the Division of Over-the-Counter (OTC) Drug Products regarding draft comments on the proposed labeling for the subject product, about which Schering-Plough HealthCare Products (SPHCP) was asked to respond prior to a September 14, 1998 joint meeting of the four FDA divisions (i.e. Special Pathogens, OTC, DDMAC, and Compliance) responsible for review and approval of this OTC labeling.

Background:
On May 19, 1998, the sponsors of the subject new drug application, SPHCP and Taro Pharmaceuticals Inc., formally requested a meeting with the appropriate FDA divisions to discuss the proposed labeling for the Gyne-Lotrimin 3® 3-Day Vaginal Cream product. The Agency denied the request because the review of the NDA was not sufficiently advanced to justify a meeting at that time. Subsequently, Dr. Christina Chi advised SPHCP that the appropriate FDA divisions should be ready to meet with us mid-September (tentative dates: September 16 or 17, 1998) to discuss labeling. We then submitted another formal request for this meeting on July 30, 1998. On September 10, SPHCP received the labeling comments noted above.

On September 11, 1998, SPHCP notified Dr. Christina Chi (DSPIDP) that we would comply with the Agency's comments on the carton and educational brochure, but could not comply with their suggested label changes for the 21 gram tube because of insufficient space on the label to bear the requested information. SPHCP requested that the Agency reconsider our original proposed tube label which had been prepared based on the most recently approved tube label for a vaginal antifungal cream (i.e., Femstat ®3 Cream, butoconazole nitrate vaginal cream, 20 grams) and met the small package labeling requirements per 21 CFR § 201.10 (h)(2)(i).

Following the Agency's September 14, 1998 meeting, Dr. Chi informed SPHCP that FDA had accepted our proposal to decrease the requirements for the tube label and would need two weeks to revise it. The four reviewing divisions were to again meet jointly on September 30, 1998, and would send us their joint final labeling recommendations via facsimile. This resulted in the FDA canceling the planned September 17, 1998, meeting to discuss the subject labeling with the sponsors. Subsequently, we were further informed that due to scheduling conflicts, the four FDA reviewing divisions would not meet on September 30, 1998, but instead the OTC Division would obtain each Division's comments on the proposed labeling and provide SPHCP with the Agency's final joint recommendations in the near future.

Sponsor's Labeling Comments:
Because we did not have the opportunity to meet with the Agency as planned on September 17, 1998, to discuss our proposed labeling and the Agency's comments in detail, we are herein providing our position and concerns with regard to the Agency's draft comments of September 10, 1998.

Tube Label

Unlike the 45 gram tube of clotrimazole vaginal cream 1% (marketed under NDA 18-052 for a 7 day treatment of vulvovaginal candidiasis), the subject product consists of a much smaller tube (21 gram) which is unable to accommodate the same amount of information as the 45 gram tube. Instead, the labeling proposed by SPHCP for the 21 gram tube meets the requirements for a small package size as allowed under §201.10 (h)(2)(i) which states:

> "a drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1)(A)(ii) and (B) of the act shall be exempt from compliance with those clauses: Provided, That: (1) The label bears: (i) The proprietary name of the drug; (ii) The established name, if such there be, of the drug: (iii) An identifying lot or control number; and (iv) The name of the manufacturer, packer, or distributor of the drug; and (2) All the information required to appear on the label by the act and the regulations in this chapter appears on the carton or other outer container or wrapper if such carton, outer container or wrapper has sufficient space to bear such information, or such complete label information appears on a leaflet with the package."

In conformity with the above, SPHCP included all of the required labeling for a small package size in preparing the tube label. Because space permitted, additional information similar to that which was approved for the Femstat ®3 Cream 20 gram tube was also included (e.g., a statement to read the warning information on the carton or in the educational brochure before using the product). Full labeling appears on the product carton as well as in the educational brochure. Finally, because this package includes three disposable cardboard applicators rather than individually wrapped pre-filled applicators, SPHCP is confident that the consumer will retain the carton with full labeling for the duration of the three day treatment as a convenient place to store the tube and applicators.

General Recommendations

Although SPHCP has agreed to comply with the changes recommended by the Agency on the carton and brochure contained in the September 10, 1998 facsimile, we are in disagreement with several specific recommendations made for the labeling and would like the Agency to consider the following :

Active Ingredient

SPHCP version: *Clotrimazole (2%) (100 mg per 5 g dose)*

FDA version: *Clotrimazole Vaginal Cream (2%) (100 mg per applicator)*

The Agency has requested that we use the "full USP name of the active ingredient "Clotrimazole Vaginal Cream (2%)." However, under 21 CFR § 314.3 (b), a drug substance is defined as an "active ingredient that is intended to furnish pharmacological activity...." and a drug product is defined as a " finished dosage form ...that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." Therefore, the proper USP name of the *active ingredient* (i.e. drug substance) contained in the subject product is "clotrimazole (2%)", not "Clotrimazole vaginal cream (2%)" which is the full USP name of the *drug product.*

It is especially important to make this distinction when the active ingredient is followed by the amount provided per dose. For example, in the subject product each applicator provides *5 grams of the clotrimazole vaginal cream (drug product)*, which contains *100 mg of clotrimazole (active ingredient)*. In other words, the FDA version listed above is incorrect in the use of "clotrimazole vaginal cream" as an active ingredient and compounds this error by stating that the applicator contains 100 mg of clotrimazole vaginal cream, rather than the true 5 gram quantity.

Net Contents

SPHCP version: *One 21g (0.74 oz.) Tube of Clotrimazole Vaginal Cream (2%) and 3 Disposable Applicators*

FDA version: *One 21g (0.74 oz.) Tube of Vaginal Cream (Clotrimazole Vaginal Cream (2%) (100 mg per applicator)) and 3 Disposable Applicators*

Similarly, we disagree with the use of "100 mg per applicator" in conjunction with "Clotrimazole Vaginal Cream" as part of the net contents statement for the reasons explained above. In addition, SPHCP feels that the inclusion of this information under net contents would be confusing to the consumer who uses the net contents for value comparisons of products. Lastly, the SPHCP version eliminates the repetition of "vaginal cream" conserving valuable space on both the carton and the tube label.

Our final concern is with the change on the principal display panel which replaced the words "Vaginal Cream" with "3 Disposable Applicators." This statement is placed in a bar across the package front to help the consumer distinguish between our 3-day products, i.e., inserts, combination pack, and cream. (See attached graphic examples.)

In view of the protracted nature of these labeling discussions and the benefit to both FDA and SPHCP from a prompt resolution of the remaining issues, we ask that final consolidated comments be provided as soon as possible.

Sincerely,

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

mw
filed in duplicate
Desk copy: Dr. C. Chi; Dr. L. Katz; Ms. K. Lechter; Dr. B. Leissa; Ms. C. Turner; Ms. S. Walther; Dr. J. Winfield

HFD-590-Chi
9/24/98

Schering-Plough
HealthCare Products

To Distribution

From Ms. Mary Williams

Date 9/24/98

Subject Gyne-Lotrimin 3® 3-Day Cream (NDA 20-574) - Labeling Comments

---

Please find the attached desk copy of Schering-Plough HealthCare Products (SPHCP) response to the draft comments we received in a September 10,1998, facsimile from FDA, which is being concurrently submitted to the subject NDA. We are providing these desk copies for your consideration at the next joint meeting of the four divisions responsible for reviewing and approving the labeling for the subject product.

Please don't hesitate to call me at (908) 604-1952 if you have any questions. Thank you for your prompt attention to this matter.

Mary Williams

Distribution:

Dr. C. Chi
Dr. L. Katz
Ms. K. Lechter
Dr. B. Leissa
Ms. C. Turner
Ms. S. Walther
Dr. J. Winfield

Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
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October 1, 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

ADDITIONAL INFORMATION ON POSTMARKETING HISTORY AND ADVERSE EVENTS

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

Dear Dr. Goldberger:

On August 26, 1998, Schering-Plough HealthCare Products (SPHCP) submitted information in response to a request made by Dr. Ling Chin (Division of OTC Drug Products) on the marketing history of clotrimazole vaginal cream products. On September 18, 1998, SPHCP received a follow-up request from Dr. Chin for additional detailed post marketing and adverse events information which we are herein providing.

For ease of review, Dr. Chin's requests are listed in italics below and are followed by our response.

1) *Please supply the total number as well as the names of countries where clotrimazole 1% and 2% are marketed OTC. Please list the month and year (launch date) of OTC marketing.*

We were unable to retrieve all of the requested information despite numerous database searches. However, the Nonprescription Drug Manufacturers Association (NDMA) provided us with a listing of the status (prescription or nonprescription) of a number of antifungals, including clotrimazole, from 21 countries. This information was compiled in December 1997, by the World Self-Medication Industry (the world federation of nonprescription drug industry associations which includes roughly 60 countries) and AESGP (the European Proprietary Medicine Manufacturers Association - the federation of European nonprescription drug industry associations). Twelve (12) of the 14 countries

in the European Union were included in this compilation (Luxembourg and Greece were not included; the former relies on Belgium or the Netherlands; the latter has no meaningful OTC classification), as well as 9 other countries from around the world. Of the 21 countries included in the compilation, the following 12 countries market an OTC clotrimazole vaginal product: (Note, the year in which the Rx-to-OTC switch occured is provided when available. See Attachment 1 for the complete compilation of Rx and OTC classification of antifungals provided by NDMA.)

<u>European Union</u>	
Denmark (1996)	Ireland (1997)
France	Sweden (1994)
Germany (1994)	United Kingdom (1992)
<u>Other Countries</u>	
Norway (1995)	Korea
Australia	New Zealand
Canada	USA (1990)

2) *Please supply supporting information of the AEs pertinent to Schering's clotrimazole vaginal cream product:*

(a) the serious case of the 94-year old woman with pyelonephritis,

(b) the case reports of all the other AEs, especially the ones involving the body as a whole, skin and application site, female reproductive system, and urinary system.

(a) This case was reported in 1987 when the product was still marketed as an Rx product. All of our New Jersey records from that period were in archives and were destroyed in a fire several years ago. Records of our Consumer Relations group in Memphis are kept for seven years, and so no further information is available for this case. At the time, the event was considered unlikely related.

(b) We are attaching the MedWatch forms by categories, as follows: "disorders of the reproductive system," "renal and urinary system disorders," "application site disorders," and "therapeutic response decrease" (see answer to #3 below). ***Please note that most of these reports are duplicates or triplicates, as their complaints are overlapping, i.e., most of the reports contain events from more than one of the above mentioned categories, as these events are linked (i.e. vaginitis, application site reaction, therapeutic response decrease).***

<u>Disorders of the reproductive system:</u> the overwhelming majority of these cases are coded as vaginitis (mainly irritation). Most of these cases are seen in consumers who reported that the product wasn't effective, and these cases seem

to represent symptoms of the underlying disease. A few cases of slight vaginal bleeding or perceived intermenstrual bleeding have been coded as vaginal hemorrhage.

Most of these cases have been reported by the consumers, a few by physicians (mainly while the drug was still a prescription drug) or pharmacists, and one case of vaginitis was reported through an attorney. One of the cases was a spontaneous abortion (reported as a 15 Day - Fetal Death) in a patient who had experienced a previous spontaneous abortion and had blood type Rh(-), while her husband was Rh(+) [case 92-12-202].

Application site disorders: most of these cases mention burning, some mention pain or irritation.. Once again, the vast majority of cases were reported by consumers, very few by physicians or pharmacists (while the drug still was a prescription drug).

Renal and urinary system disorders: only 3 of these cases were reported, all of them by consumers: one intercurrent, and 2 micturition disorders (both of them resolved spontaneously).

The *Body as a whole* MedWatch forms are not provided, as the bulk of these cases are the therapeutic response decrease cases (described below in response #3), with only some individual non-specific cases of fever, fatigue, headache, malaise, influenza-like symptoms edema, dizziness, chest pain, asthenia, reaction non specific etc.

3) *Please provide an explanation for the occurrence (i.e. consumer complaints of dissatisfaction with product, seeking refund, etc.) of the AEs reported as therapeutic response decreases.*

All cases reported as *therapeutic response decrease* came from consumers. Almost 100% of them were seeking a refund, which is typical of the OTC drug market. For all of these cases, there is no certainty of the initial diagnosis or the outcome, and even though consumers are sent follow-up questionnaires to gather more information, only a minority of them respond.

The overall frequency of these reports is approximately 1 report or less per [redacted] tubes of cream sold. However, the increase in the frequency of these reports seen in the first few years of OTC marketing has been steadily decreasing, and for the last several years the frequency has been approximately 1 complaint per [redacted] tubes of cream sold. In addition, the frequency of the therapeutic response decrease reports for the 1%

clotrimazole vaginal cream is comparable to that received for other OTC products. It is also important to keep in mind that the overwhelming majority of the therapeutic response decrease reports are based only on the consumer's perception. Most consumers asked for a refund, or in some cases asked for a second tube of cream and then reported satisfactory results. In other cases, consumers reported lack of effectiveness because of persistence of a symptom like itching, which is well recognized as potentially remaining for several days, even in the presence of a successful treatment. Given all of this information, and given the demonstrated effectiveness of this product in rigorously designed controlled clinical trials, SPHCP concludes that there is no safety concern regarding the therapeutic response decrease reports for clotrimazole vaginal cream.

We trust this information adequately demonstrates the safety of OTC marketing of the subject product. 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
filed in duplicate
Desk copies: Dr. Ling Chin, Dr. Christina Chi

Arc to Dr Kim, this arrived at 2:30 PM
C. Chi picked it up at 5:00 PM in the DCC

Schering-Plough
HealthCare Products

Dr. Chi

Receipted Copy

Schering-Plough Corporation
110 Allen Road
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Liberty Corner, New Jersey 07938-0276
Telephone (908) 604-1640
Fax (908) 6[illegible]

October 16, 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

PRE-MEETING INFORMATION ON TUBE LABELING

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: GENERAL CORRESPONDENCE

Dear Dr. Goldberger:

We are herein providing information on the rationale for use of the Schering-Plough HealthCare Products' (SPHCP) proposed tube labeling for launch of the subject product, which will be discussed in greater detail at an October 21, 1998, meeting with the Agency.

Background

On October 6, 1998, SPHCP notified the Agency that we agreed to incorporate all of the changes outlined in the final version of labeling for the subject product, as reviewed by the DOTCDP, sent to us earlier that day via facsimile. The artwork process was immediately initiated in order to provide the Agency with the requested final colored mock-up labels with these changes for its review and signature at an internal Agency meeting on October 21, 1998.

However, at the same time that SPHCP notified the Agency of our commitment to implement its proposed labeling, we also sought to speak with key FDA personnel on a critical issue involving the tube label. Believing the issue to be better addressed in a face-to-face meeting, we asked to speak with the Agency in person at their scheduled October 21, 1998 meeting instead of in a teleconference.

Action Requested

Following approval of the subject NDA, Schering-Plough HealthCare Products requests permission to market Gyne-Lotrimin 3® Vaginal Cream with the tube label previously proposed by SPHCP for the initial launch of the product. The FDA tube label will then be used for any Gyne-Lotrimin 3® Vaginal Cream product shipped after April 1999, the projected date of availability for this printed tube.

Rationale

The SPHCP proposed tube label meets the requirements for a small package size as allowed under §201.10 (h)(2)(i). Unlike other marketed vaginal cream products for 3-day treatment which are packaged in pre-filled applicators, and provide minimum labeling on the overwrap, SPHCP included additional labeling information on its proposed tube label similar to that which was approved for the Femstat ®3 Cream 20 gram tube.

Importantly, when compared to the FDA proposed tube label, all of the information relevant to the consumer is essentially the same on both the proposed SPHCP and FDA tube labels. This is readily apparent in the side by side comparison of SPHCP's proposed tube label to FDA's tube label presented in Attachment I, in both a single page containing the entire labels in the proposed order and format, and separate pages highlighting each label component. Other than minor changes in the wording of some of the statements and in the order of information, the only significant difference between the labels is FDA's addition of the statement regarding first time use. However, this identical statement is prominently displayed on the product carton which is read by the consumer at the point of purchase, and a similar but more detailed statement is contained in the educational brochure. A warning statement on both versions of the tube instructs the consumer to read these pieces before using the product. At the meeting on October 21, 1998, SPHCP will present results of recent consumer research supporting our position that that the key messages of both tube labels are the same.

Because the Gyne-Lotrimin 3 Vaginal Cream product includes three disposable cardboard applicators (rather than individually wrapped pre-filled applicators) SPHCP is confident that the consumer will retain the carton with full labeling for the duration of the short three-day treatment as a convenient place to store the tube and applicators. Hence the full labeling is most likely to be available throughout the treatment period.

In order to be in a ready position to launch the product around the time of its expected approval, and due to the lengthy lead time for tube availability a quantity of [redacted] units of tubes had to be ordered to cover the estimated volume needed for launch [redacted]

In previous discussions between SPHCP and the FDA, as well as in FDA Dialogue Sessions with the Industry, the Agency has been made aware of the logistical difficulties in obtaining printed tubes for a marketed product. [redacted]

Requiring the FDA proposed tube labeling to be used will delay launch of this product for some 4 to 5 months after approval and eliminate a significant portion of the product exclusivity period.

In addition to the extensive lead time for obtaining the printed tubes, there was also concern over the availability of a resin used in the head of the tube, which the vendor informed us was being discontinued. This resin is used in 15 Schering-Plough products marketed under NDAs and numerous other products marketed under the drug monograph system. In an agreement with the FDA, an "Expedited Review Requested" supplement was sent to each of these NDAs under the bundling review policy. However, the subject NDA was not included in this process, in order not to delay its approval. A supplement for the new resin will be submitted post-approval. Schering-Plough proceeded to order the tubes containing the discontinued resin using our proposed labeling. Had we not ordered at that time, we would have risked being in an out-of-stock position at the time of expected approval.

In view of the extenuating circumstances, the minor differences in labeling and the clear parity in message based on consumer testing, we trust that the above information concerning the practically identical messages in the proposed FDA and SPHCP tube labeling, as well as the critical business issue at stake, will be helpful in your consideration of the request to market our proposed tube labeling for the limited period of time being sought. Thank you for the opportunity to meet with you on October 21, 1998 to discuss further.

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
filed in duplicate
Desk copy: Dr. Christina Chi

Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
PO Box 276
Liberty Corner, New Jersey 07938-0276
Telephone [illegible] 1640
Fax (90[illegible] 1848

October 16, 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: LABELING-COLORED COPIES

Dear Dr. Chi:

Enclosed, please find colored mock-up labeling (22 copies each of the tube, carton, and educational brochure) for the subject product as requested for Agency review and signature. In addition, copies of this colored mock-up labeling are being concurrently sent to Ms. Karen Lechter and Ms. Joanne Spearmon in the Division of Drug Marketing, Advertising and Communications, as well as to Mr. William Nychis and Mr. Robert Eshelman in the Office of Compliance for their review.

The labeling for this product has been revised again based on your October 6, 1998 facsimile of the final version of labeling as reviewed by the DOTCDP.

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.

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

attachments
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bc

Schering-Plough
HealthCare Products

October 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

RESPONSE TO CMC COMMENT ON DRUG SUBSTANCE

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: CMC AMENDMENT

Dear Dr. Goldberger:

This is in response to a chemistry, manufacturing, and controls (CMC) comment on the drug substance, clotrimazole, which we received via facsimile from Dr. Dorota Matecka on October 7, 1998. For ease of review, Dr. Matecka's comment is provided below, followed by Schering-Plough HealthCare Products' (SPHCP) response.

FDA Comment

Please propose acceptance criteria for the drug substance, clotrimazole, that include specifications for impurities (single unknown impurity, sum of unknown impurities and sum of all impurities) and specifications for residual solvents.

SPHCP Response

(1) A method for the Estimation of Chromatographic Impurities has been developed by our Research and Development Analytical laboratory as part of our corporate wide Product Quality Review Program. This analytical method for impurities is being transferred to our Quality Control Laboratories. Following the transfer of this method to Quality Control, it will be utilized to generate data on incoming material over a twelve month period in order to develop a database from which final regulatory specifications will be established. During this period the specifications will be "Report as Found" (see example below). It is our intent to establish this method as a Regulatory method with final specifications, following the review of the data generated during a twelve month period, through a Prior Approval supplement.

(example)

Chromatographic Impurities	SPECIFICATION
Specified Knowns	
[redacted]	
Unspecified Others	
Individuals	Report as Found
Total	Report as Found
Total Specified and Unspecified	Report as Found

(2) Two Schering general test procedures for determination of residual solvents in a drug substance are being utilized to detect the presence of residual solvents in the clotrimazole drug substance. [redacted] When an analytical method for residual solvents in the drug substance clotrimazole has been fully developed, it will be also be transferred to our Quality Control Laboratories, as described above for the impurities analytical method. Again, following the transfer of the method to Quality Control, the residual solvent method will be utilized to generate data on incoming material over a twelve month period in order to develop a database from which final regulatory specifications will be established. During this period the specifications will be "Report as Found". It is our intent to establish the residual solvent method as a Regulatory method with final specifications, following the review of the data generated during this twelve month period, through a Prior Approval supplement

We are enclosing the following analytical methods for your information only. When the specifications have been determined, the final analytical method for impurities and the final analytical method for residual solvents will be included in the Prior Approval supplement.

[redacted]

We trust this information adequately addresses your request. Please don't hesitate to contact me at (908) 604-1962 if you have any questions or require further information.

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 for/

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

mw
filed in duplicate
Desk copy: Dr. Christina Chi

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October 28, 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: CMC AMENDMENT

Dear Dr. Chi:

Enclosed, please find your personal desk copy of the amendment being concurrently submitted to the subject NDA. This submission provides APE data at the 31 month test interval for an additional batch which was included in our August 7, 1998 amendment.

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 information, please don't hesitate to contact me at (908)604-1952.

Sincerely,

Mary E. Williams

Mary E. Williams
Associate Director Regulatory Affairs

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October 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

Antimicrobial Preservative Effectiveness Test Results

SUBJECT: NDA # 20-574, Gyne-Lotrimin 3® 3-Day Vaginal Cream
CMC AMENDMENT

Dear Dr. Goldberger:

As promised in our August 7, 1998, amendment to the subject NDA, we are herein providing the results of the Antimicrobial Preservative Effectiveness (APE) test for Batch [redacted] conducted at a 31 month interval.

Background

On July 22, 1998, we received comments from Ms. Patricia Hughes (FDA microbiologist reviewer) on the APE test data for the subject NDA, which were discussed in a July 27, 1998, teleconference with the Agency. On August 7, 1998, Schering-Plough HealthCare Products (SPHCP) submitted an amendment to the application, which included the minutes of the teleconference and the agreements reached with the Agency, as well as APE and stability data on an additional batch as promised.

Because the stability studies for the additional batch (manufactured in September 1995) had been placed on hold when the NDA was withdrawn in January 1996, testing was not conducted at all of the time-points listed in the stability protocol. Therefore, results of APE tests conducted only at the initial and 3 month time intervals were included in the stability report provided in the amendment, with a commitment to submit the results of an APE test for a 31 month interval as soon as they became available.

Results

A copy of SPHCP's current APE protocol, which had been modified to comply with USP 23, Supplement 8, (official May 15, 1998) was provided in the August 7, 1998 amendment. Results of the APE test on Batch [redacted] at a 31 month interval demonstrate that the product

meets USP Preservative Effectiveness criteria for Category 1B Products ("Topically used products made with aqueous bases or vehicles, nonsterile nasal products, and emulsions, including those applied to mucous membranes." USP 23, Supplement 8). Full details of the test results are provided in the attached page.

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 trust this information satisfies all of your requirements for APE testing of the subject product. Please don't hesiatate to contact me at (908) 604-1962 if you have any additional questions regarding this matter. Thank you.

Sincerely,

Mary E. Williams /for

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

mw
filed in duplicate
Desk copy: Dr. Christina Chi

DUPLICATE NEW CORRESP NC

Schering-Plough HealthCare Products

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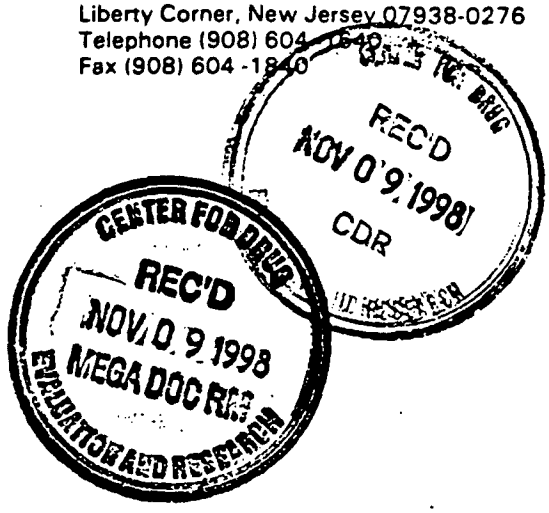

November 6, 1998

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:

Schering-Plough HealthCare Products (SPHCP) is herein providing information to the subject new drug application which had been previously sent to Dr. Christina Chi via facsimiles (3). This information pertains to SPHCP's commitment to incorporate all of the labeling changes outlined in a 10/6/98 facsimile received from the Agency, as well as a request to meet with the Agency to discuss a special situation regarding the tube.

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 information, please don't hesitate to contact me at (908) 604-1962. Thank you.

Sincerely,

Mary E. Williams /for

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

mw
filed in duplicate
attached: two facsimiles from 10/6/98 and one facsimile form 10/8/98
desk copy: Dr. Christina Chi

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HealthCare Products

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November 6, 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: Phase IV Commitments

Dear Dr. Chi:

Enclosed, please find your personal desk copy of the correspondence being concurrently submitted to the subject NDA.

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

Mary E. Williams
Associate Director Regulatory Affairs

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HealthCare Products

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Fax (908) 604-1840

November 10, 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 your personal desk copy of the correspondences (2) being concurrently submitted to the subject NDA.

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

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 10, 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:

Schering-Plough HealthCare Products (SPHCP) is herein providing information to the subject new drug application which was previously submitted informally to Dr. Joseph Winfield, the Medical Review Officer, via facsimile.

On September 22, 1998, Dr. Winfield requested a listing of all patients from clinical studies 93-34 and 93-40 who were included in our June 11, 1998 submission as "non-evaluable" due to missing data at Visit 3. This information was sent to Dr. Winfield on September 23, 1998. In subsequent discussions it was determined that, based on the protocol evaluation criteria, some of these patients should have been considered "evaluable" and categorized as either therapeutic cures or therapeutic failures, and included as such in the final statistical analysis.

We are in agreement with the approach taken by Dr. Winfield in his final categorization of these patients which will be included in his medical report.

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 there are additional questions, please don't hesitate to contact me at (908) 604-1962.

Sincerely,

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

mw: filed in duplicate: desk copy - Dr. Christina Chi

Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
P.O. Box 276
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Telephone (908) 904-2640
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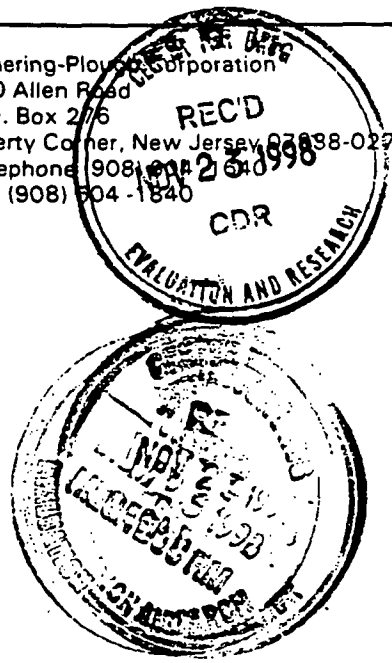

November 20, 1998

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:

We are herein submitting Schering-Plough HealthCare Products' minutes from the October 21, 1998, meeting with the Agency regarding labeling for the subject product. In turn, we request that the Agency provide us with their record of minutes for this meeting as soon as they become available.

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 /for

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

mw
attachment
desk copy: Dr. Christina Chi

Schering-Plough
HealthCare Products

Schering-Plough Corporation
110 Allen Road
P.O. Box 276
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Telephone (908) 604-1640
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November 30, 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
Comments on Final Approved Labeling

SUBJECT: Gyne-Lotrimin 3® 3-Day Vaginal Cream
NDA # 20-574: Correspondence

Dear Dr. Chi:

As discussed in a telephone call which I placed to you on November 24, 1998, immediately following receipt of the approval letter for the subject NDA, Schering-Plough HealthCare Products (SPHCP) is herein providing comments on the final approved labeling which was included in the approval letter. For ease of review, the statement in the approval letter being addressed is provided below in italics, and followed by SPHCP's comments.

1. *The approved labeling text for the carton and educational brochure is specified in Attachment A.*

• Based on an understanding reached with the Agency in our October 21, 1998, meeting, and as noted in the Agency's October 29, 1998, facsimile, as well as in item #3. of the approval letter, the following statement in both the carton and educational brochure specified in Attachment A should be deleted: "If you have any other questions, or need more information on this product, call our **TOLL-FREE Number at 1-8XX-(XXX-XXXX)**, between 8:00 a.m. and 5:00 p.m. Eastern Standard Time, Monday through Friday." Please note: as previously discussed, SPHCP is in the process of establishing a toll-free number and has agreed to add this statement to the label within 12 months of the NDA approval.

• In addition, two of the diagrams in the "The "Directions for Use" section of the educational brochure had been slightly modified and provided to the Agency for review prior to the October 21, 1998, meeting. The discrepancies between the directions for use in the educational brochure provided in Attachment A of the FDA approval letter, and those which will be used by SPHCP for the initial launch period, are noted below:

"2. Attach the applicator to the tube of cream by placing ~~"A"~~ end of the applicator firmly onto tube of cream. (See picture.)" (Note: the "A" has been deleted from the text and the diagram in the SPHCP labeling for initial launch.)

"3. Gently squeeze the cream into the applicator, continue squeezing until line on plunger (P) marked "FULL" reaches end of barrel (B)." (Note: the (P) and (B) have been added to the text and the diagram in the SPHCP labeling for initial launch.)

As discussed, it is our understanding that you will bring these discrepancies to the attention of the DOTCDP, who will address them in an amendment to the approval letter.

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

Mary E. Williams
Associate Director Regulatory Affairs