

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-143**

**CORRESPONDENCE**

**Schering-Plough  
HealthCare Products**

February 19, 1999

Schering-Plough Corporation  
110 Allen Road  
P.O. Box 276  
Liberty Corner, New Jersey 07936-0276  
Telephone (908) 604-1640  
Fax (908) 604-1840

Debra Bowen, M.D., Acting Director  
Division of OTC Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
HFD-560  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, MD 20850

Alternative Manufacturing Site

Subject: NDA 20-574; Gyne-Lotrimin3® 3-Day Vaginal Cream  
(clotrimazole vaginal cream, 2%)  
GENERAL CORRESPONDENCE

Dear Dr. Bowen:

Schering-Plough HealthCare Products (SPHCP) is herein requesting guidance on the requirements for approval to concurrently market a Taro Pharmaceuticals Inc. clotrimazole vaginal cream, 2% product, similar to the approved SPHCP product, under the subject NDA.

Background: SPHCP and Taro co-sponsored the clinical studies provided in the recently approved subject NDA. One of the two pivotal clinical studies used to demonstrate the safety and efficacy of the clotrimazole vaginal cream, 2% product for a 3-day vaginal antifungal treatment was conducted by Taro. The formula used in the Taro study was the same as that marketed in Canada by Taro since 1989. At FDA's request, a bridge study comparing the slightly different SPHCP and Taro formulations was conducted. The results, which FDA agreed demonstrated the equivalency of the two formulations, were provided to the NDA.

The SPHCP facility in Manati, PR, is the approved manufacturing site for the subject product. As part of the original joint business venture between SPHCP and Taro, SPHCP is required to manufacture the subject product for Taro distribution in the USA at a future date. However, both companies have subsequently determined that it is more economically advantageous for each company to concurrently manufacture and market their own product, i.e., Taro to manufacture and market their existing Canadian product in the USA, and SPHCP to continue manufacture and market the product as currently approved in the NDA.

To determine the best way to accomplish this, a call was placed to your Ms. Elizabeth Yuan, followed by a SPHCP facsimile on January 22, 1999, requesting FDA guidance on this matter. (See attached facsimile copy.) On February 12, 1999, SPHCP received a facsimile from the DOTCP Chemist Reviewers requesting the following comparative information "in order to fully understand the scope of the intended change:"

NDA 20-574  
Gyne-Lotrimin3® 3-Day Vaginal Cream

2/19/99  
Page 2

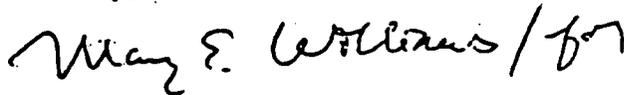
- 1) **Current Formulation:** A table comparing the two formulas is provided in Attachment 1, followed by the specification for an inactive ingredient which slightly differs in the formulas.
- 2) **Method of Manufacture for the product:** An outline of the SPHCP and Taro manufacturing processes and the major differences is provided in Attachment 2.
- 3) **Specifications and methodology:** General information for the drug substance, inactive ingredients, and drug product is provided in Attachment 3.
- 4) **Container/ closure system:** A description of the SPHCP and Taro packaging components is provided in Attachment 4.
- 5) **Labeling:** The labeling for both of the formulations will be identical to that specified in the approved NDA with the exception of the brand name and place of manufacture.

**Proposal:** One possible approach would be to handle the submission as a 505(b)(2) application consisting of complete CMC information for the Taro product and a reference to the clinical studies contained in the subject NDA. We believe this would allow both products to be concurrently marketed in the USA under the exclusivity granted for the subject NDA.

We trust that the enclosed comparative information is sufficient to enable you to provide us with the guidance we seek and look forward to discussing this matter further with you following your Team meeting scheduled for Monday, February 22, 1999.

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,



John M. Clayton, Ph.D.  
Senior Vice President, Scientific and Regulatory Affairs

filed in duplicate  
faxed to Ms. Yuan  
attachments



Schering-Plough  
HealthCare Products

March 26, 1999

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

Debra Bowen, M.D., Acting Director  
Division of OTC Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research  
HFD-560  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, MD 20850

Minutes of 3/19/99 Teleconference

Subject: NDA 20-574; Gyne-Lotrimin<sup>3</sup>® 3-Day Vaginal Cream  
(clotrimazole vaginal cream, 2%)  
GENERAL CORRESPONDENCE

Dear Dr. Bowen:

Enclosed, please find the Schering-Plough HealthCare Products (SPHCP) minutes from the March 19, 1999, teleconference with the Agency regarding FDA guidance on the requirements for approval to concurrently market two similar clotrimazole vaginal cream, 2%, products in the USA. In turn, we request that the Agency provide us with their record of minutes for this meeting per MaPP 4512.1.

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

attachment  
Faxed desk copy: Ms. Elizabeth Yuan

0002



Schering-Plough  
HealthCare Products

May 27, 1999

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  
9201 Corporate Boulevard  
Rockville, MD 20850

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

**Gyne-Lotrimin 3<sup>o</sup> 3-Day Vaginal Cream**  
**NDA # 20-574**

**SUBJECT: GENERAL CORRESPONDENCE**  
**Right of Reference to Safety and Efficacy Data**

Dear Dr. Goldberger:

Schering-Plough HealthCare Products (SPHCP) hereby grants Taro Pharmaceuticals Inc. the right of reference to all safety and efficacy data (including preclinical, toxicology, and clinical data) contained in the recently approved NDA # 20-574 for Gyne-Lotrimin 3<sup>o</sup> 3-Day Vaginal Cream, in support of a related new drug application to be submitted by Taro to the Agency. In addition, SPHCP waives the exclusivity granted the subject NDA specifically to Taro. If Taro's formulation is approved under 505(b)(1) of the Food, Drug, and Cosmetic Act, then they will be granted the remainder of SPHCP's exclusivity until November 24, 2001 under the "umbrella policy." (Page 28897, FR Vol. 54 No. 130, July 10, 1989.)

Reference is made to a March 19, 1999, teleconference (FDA minutes attached) between the Agency, SPHCP, and Taro, in which the Agency provided guidance on the requirements to concurrently market Taro's Canadian clotrimazole vaginal cream, 2%, formulation and SPHCP's recently approved clotrimazole vaginal cream, 2%, in the USA. Of the several options presented by the Agency during the teleconference, a joint SPHCP and Taro decision was made for Taro to file an original NDA under 505(b)(1), which would contain Taro's CMC information and a reference to the safety and efficacy data contained in SPHCP's NDA #20-574. This submission is subject to one-half of the full User Fee and a 12 month review.

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

attachment  
Desk copy: Dr. Christina Chi

0032



Schering-Plough  
HealthCare Products

May 27, 1999

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  
9201 Corporate Boulevard  
Rockville, MD 20850

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

**Gyne-Lotrimin 3<sup>o</sup> 3-Day Vaginal Cream**  
**NDA # 20-574**

**SUBJECT: GENERAL CORRESPONDENCE**  
**Right of Reference to Safety and Efficacy Data**

Dear Dr. Goldberger:

Schering-Plough HealthCare Products (SPHCP) hereby grants Taro Pharmaceuticals Inc. the right of reference to all safety and efficacy data (including preclinical, toxicology, and clinical data) contained in the recently approved NDA # 20-574 for Gyne-Lotrimin 3<sup>o</sup> 3-Day Vaginal Cream, in support of a related new drug application to be submitted by Taro to the Agency. In addition, SPHCP waives the exclusivity granted the subject NDA specifically to Taro. If Taro's formulation is approved under 505(b)(1) of the Food, Drug, and Cosmetic Act, then they will be granted the remainder of SPHCP's exclusivity until November 24, 2001 under the "umbrella policy." (Page 28897, FR Vol. 54 No. 130, July 10, 1989.)

Reference is made to a March 19, 1999, teleconference (FDA minutes attached) between the Agency, SPHCP, and Taro, in which the Agency provided guidance on the requirements to concurrently market Taro's Canadian clotrimazole vaginal cream, 2%, formulation and SPHCP's recently approved clotrimazole vaginal cream, 2%, in the USA. Of the several options presented by the Agency during the teleconference, a joint SPHCP and Taro decision was made for Taro to file an original NDA under 505(b)(1), which would contain Taro's CMC information and a reference to the safety and efficacy data contained in SPHCP's NDA #20-574. This submission is subject to one-half of the full User Fee and a 12 month review.

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

attachment  
Desk copy: Dr. Christina Chi

0459



TARO PHARMACEUTICALS INC.  
130 EAST DRIVE  
BRAMALEA, ONTARIO  
L6T 1C3

June 10, 1999

Mellon Bank  
Three Mellon Bank Center, 27<sup>th</sup> Floor  
(FDA360909)  
Pittsburgh, PA 15259-0001

**Re: Application Fee for  
Clotrimazole Vaginal Cream USP, 2%  
NDA # 21-143 - User Fee ID # 3731**

Dear Sir/Madam:

In reference to the above mentioned NDA, we are hereby submitting a payment for the application fee in accordance with the fee rates for FY 1999.

Please find enclosed a cheque for [redacted] payable to the US Food and Drug Administration. A copy of the User Fee Cover Sheet is also enclosed.

Should you have any questions related to this, please do not hesitate to call the undersigned at (905) 791-8276.

Sincerely Yours,  
Taro Pharmaceuticals Inc.

Derek Ganes, Ph.D.  
Vice President, Regulatory Affairs

0026

TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-4767  
905-791-5008



Stamp date:

June 17, 1999

60 day: 2/16/99

Goal: 2/17/2000

ODS: 4/7/2000

Secondary: 6/17/2000

TARO PHARMACEUTICALS INC.  
130 EAST DRIVE  
BRAMALEA, ONTARIO  
L6T 1C3

June 16, 1999

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologic Drug Products  
HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: New Drug Application for  
Clotrimazole Vaginal Cream USP, 2%  
NDA # 21-143 - User Fee ID # 3731**

Dear Sir/Madam:

Pursuant to 505 (b) (1) of the Food, Drug and Cosmetic Act, Taro Pharmaceuticals Inc. submits today an original New Drug Application (NDA) seeking approval to market Clotrimazole Vaginal Cream USP, 2%, which is an OTC drug product and is indicated for a three-day treatment of vaginal candidiasis.

The active substance in this drug product is Clotrimazole, USP (USP 23, Page No. 406, 407) and analyzed in accordance with the compendial requirements. Clotrimazole Cream is a USP (USP 23, Page No. 407, 408) drug product and analyzed in accordance with the compendial requirements.

This product will be marketed in 25 g tube with a re-usable applicator. Safety and efficacy of this product has already been established.

This NDA consists of the Chemistry and Manufacturing Controls (CMC) and labeling sections of the application. Taro is hereby requesting the Agency to refer to the Safety and Efficacy data (including preclinical, toxicology and clinical data) contained in the recently approved Schering-Plough Health Care Products (SPHCP) NDA # 20-574 for Gyne-Lotrimin 3<sup>®</sup>. A copy of SPHCP's letter granting Taro the right of reference to all safety and efficacy data contained in their NDA is attached.

The formulas of Gyne-Lotrimin 3<sup>®</sup> and Taro's Clotrimazole Vaginal Cream USP, 2% are slightly different. Comparison between Taro's and Schering's formulations and methods of manufacture are provided in this application.

TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-4767  
905-791-5008

Previous agreement has been made with FDA on the requirements of submission and subsequent marketing of Taro's Clotrimazole Vaginal Cream USP, 2%. It has also been agreed that this submission is subject to one-half of the full User Fee and a 12-month review time. A copy of the minutes of a teleconference of March 19, 1999 between FDA, SPHCP and Taro is attached.

Taro Pharmaceuticals Inc. is filing an archival copy (in a blue folder) a technical review copy (in a red folder) and field copy (in a burgundy folder). In addition one copy in a green ring binder is enclosed to be forwarded to Dr. Christina Chi, Project Manager, Office of Drug Evaluation IV.

Taro Pharmaceuticals Inc. hereby certifies that, the field copy of this NDA submission contained in burgundy folders is a true copy of the technical sections of the NDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the NDA.

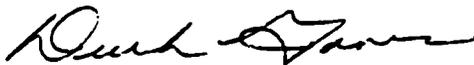
Two electronic copies on 3.5" diskettes, and four printed copies of the labeling have been included in Section F of the review copy (red folder).

In addition, one electronic copy on a 3.5" diskette and eight printed copies of the labeling are included in the "Personal Desk Copy" addressed to the attention of Dr. Christina Chi.

If there are any questions regarding this application, or if additional information is required, please contact our US agent:

Taro Pharmaceuticals USA, Inc.,  
Attn: Kalpana Rao  
Associate Director Regulatory Affairs  
5 Skyline Drive  
Hawthorne, NY 10532  
Tel: (914) 345-9001

Sincerely,  
Taro Pharmaceuticals Inc.



Derek Ganes, Ph.D.  
VP, Regulatory Affairs

/Lul Ogbaghebriel  
CC: Dr. Christina Chi

Enclosures:           **Archival Copy (2 volumes - Blue folder)**  
                              **Review Copy: (2 volumes - Red folder)**  
                              **Field Copy: (2 volumes - (Burgundy folder)**  
                              **Personal Desk Copy: (1 volume - green ring binder)**  
                              **Method Validation Package: (2 copies - red folders)**

**TARO PHARMACEUTICALS INC**  
TELEPHONE  
905-791-8276  
1-800-268-1975  
TELEFAX NO.  
905-791-5008

July 16, 1999

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Division of Special Pathogens & Immunologic drug products  
HFD - 590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

9



TARO PHARMACEUTICALS INC.  
130 EAST DRIVE  
BRAMALEA, ONTARIO  
L6T 1C3

RE: Clotrimazole Vaginal Cream, 2%  
NDA #21-143

Dear Dr. Goldberger,

Reference is made to our NDA dated June 15, 1999 for Clotrimazole Vaginal Cream USP, 2% and the facsimile correspondence from the Agency dated 6<sup>th</sup>, July 1999, in which the following was stated:

*Please confirm that the following facilities are the ONLY sites involved in the manufacturing, testing and packaging of drug substance and drug product for your NDA 21-143. Please confirm that the address and the functions listed for each site are correct, and that all the facilities are ready for the GMP inspection:*

Drug substance (clotrimazole):

Drug product (clotrimazole Vagina cream):

**Taro Pharmaceuticals Inc.**  
130 East Drive  
Bramalea, Ontario  
Canada L6T 1C3  
(manufacturing, processing, packaging)

*Please specify the function of:*

TELEPHONE  
905-791-8276  
1-800-268-1975  
TELEFAX NO.  
905-791-5008

July 16, 1999

[Redacted]

*Please provide also the respective drug establishment registration number (CFN) for each site.*

**Response:**

**Drug Substance**

- [Redacted] is the only site involved in the manufacture, testing and packaging of the drug substance Clotrimazole for the above referenced NDA.
- The correct address is:

[Redacted]

- [Redacted] is ready for GMP inspection.
- [Redacted] Drug Establishment Registration number is [Redacted]

Also, see attached confirmation from the drug substance supplier.

**Drug Product:**

- Taro Pharmaceuticals, Canada, is the only facility involved in manufacture, testing and packaging of the drug product Clotrimazole Vaginal Cream USP, 2% for the above referenced NDA.
- The address is:

**Taro Pharmaceuticals Inc.  
130 East Drive  
Bramalea, Ontario  
Canada L6T1C3**

- Taro is ready for GMP inspection. Taro would also like to make a statement that Taro's last GMP/Pre approval inspection was from June 15, 1998 to June 18, 1998, which was only one year ago, and resulted in minimal FD 483 observations and subsequently the product was approved.
- Taro's (Canada) Drug Establishment Registration number is FCCA133.

The function of:

[Redacted]

July 16, 1999

[REDACTED]

An authorized **agent/supplier** of the drug substance for [REDACTED]

If you require any further information, please do not hesitate to contact me.

Sincerely,

Kalpana Rao (US Agent)  
Associate Director, RA  
Taro Pharmaceuticals U.S.A., Inc.

**CC: Dr.Christina Chi**  
(Chief Project Manager)

**APPEARS THIS WAY  
ON ORIGINAL**

August 12, 1999



Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Division of Special Pathogens & Immunologic drug products  
HFD - 590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

9

**RE: Clotrimazole Vaginal Cream, 2%  
NDA #21-143**

**Dear Dr. Goldberger,**

Reference is made to our NDA dated June <sup>16</sup>~~15~~, 1999 for Clotrimazole Vaginal Cream USP, 2% and the verbal correspondence dated 3<sup>rd</sup>, August, 1999:

Pursuant to 21 CFR 314.94 (a) (7) we are enclosing the following:

1. "Financial Certification/Disclosure Statement - Form 3454" for Taro Pharmaceutical Inc.
2. "Financial certification/disclosure Statement - Form 3454" on behalf of Schering - Plough HealthCare products (SPHCP), co-sponsor of the studies.

If there are any questions regarding this documentation, please do not hesitate to contact me at (914) 345-9001 ext.298.

Sincerely,

*Kalpana Rao*  
8/13/99

Kalpana Rao (US Agent)  
Associate Director, RA  
Taro Pharmaceuticals U.S.A., Inc.

**CC: Dr. Christina Chi**  
(Chief Project Manager)

August 25, 1999



Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Division of Special Pathogens & Immunologic drug products  
HFD - 590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

**RE: Clotrimazole Vaginal Cream, 2%  
NDA #21-143**

**Dear Dr. Goldberger,**

Reference is made to our NDA dated June 15, 1999 for Clotrimazole Vaginal Cream USP, 2% and the verbal correspondence dated 18th, August, 1999:

Pursuant to 21 CFR 314.50 (d) (5) (vi)(b) we are enclosing the following:

1. Safety Update Information.

If there are any questions regarding this documentation, please do not hesitate to contact me at (914) 345-9001 ext.298.

Sincerely,

  
8/25/99  
Kalpana Rao (US Agent)  
Associate Director, RA  
Taro Pharmaceuticals U.S.A., Inc.

**CC: Dr. Christina Chi**  
(Chief Project Manager)

**Dr. Ling Chin, MD, MPA**  
Division Of OTC Drug products

August 25, 1999



*Handwritten initials*

Dr. Christina Chi  
Chief Project Manager  
Office of Drug Evaluation IV  
Division of Special Pathogens & Immunologic Drug products  
HFD 590, Room No N303/CRP2  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

**RE: Clotrimazole vaginal Cream USP, 2%**  
**NDA #21 143 Personal Desk Copy**

Dear Dr. Chi:

Pursuant your verbal request I am enclosing the following information regarding the above referenced NDA:

1. Copy of cover letter.
2. Safety Update Information.

If there are any questions regarding this documentation, please do not hesitate to call me at (914) 345-9001 Ext.298.

Sincerely,

*Handwritten signature: Kalpana Rao, 8/25/99*

Kalpana Rao (US Agent)  
Associate Director, RA  
Taro Pharmaceuticals U.S.A., Inc.

November 17, 1999

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Division of Special Pathogens & Immunologic drug products  
HFD - 590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850



A handwritten signature in black ink, appearing to be "R" or "S", located to the right of the TARO logo.

**RE: Clotrimazole Vaginal Cream, 2%  
NDA #21-143**

**Dear Dr. Goldberger,**

Reference is also made to our NDA dated June 15, 1999 for Clotrimazole Vaginal Cream USP, 2%:

1. Enclosed please find two (2) diskettes and four (4) draft copies of revised labeling of the above referenced drug product. Revisions are made to be similar to "Gyne Lotrimin 3 day vaginal cream".
2. Pursuant my conversation with Dr. Christina Chi, Taro Pharmaceuticals Inc. has proposed the following brand name for the above referenced NDA, and they listed based on the priority:
  - 2.1 " Gyne Clotrimin III"
  - 2.2 " Fem Clotrimin III"
3. Further correspondence with this NDA will be handled by "Lorraine Sachs", who is also an authorized US Agent.

If you have any additional questions, please feel free to contact Ms. Lorraine Sachs at 1-914-345-9001.

Sincerely,

A handwritten signature in black ink, appearing to be "Kalpana Rao", with the date "11/17/99" written below it.

Kalpana Rao (US Agent)  
Associate Director, RA  
Taro Pharmaceuticals U.S.A., Inc.

**CC: Dr.Christina Chi**  
(Chief Project Manager)

Received: 1/6/2000



January 5, 2000

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

*GH*

**Re: Amendment to NDA for  
NDA # 21-143 (Clotrimazole Vaginal Cream, 2%)**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to a phone conversation between Taro and Dr. Christina Chi of the Agency on December 14, 1999.

Dr. Chi indicated to us that the proposed names for the Taro drug product submitted on November 17, 1999 were unacceptable. Therefore, we are submitting five names for further consideration, as follows:

**Vagizole - 3**  
**Trivagizole - 3**  
**Trifemizole - 3**  
**Clofemin - 3**  
**Clotrimistat - 3**

Please notify us as to which of these names are acceptable so that we can make a final selection of a brand name prior to the submission of any labeling changes.

Sincerely,

**Taro Pharmaceuticals U.S.A., Inc.**

A handwritten signature in black ink, appearing to read "Lorraine W. Sachs".

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi



Personal Desk Copy

January 19, 2000

4

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologic Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: NDA # 21-143 (Clotrimazole Vaginal Cream, 2%)  
Labeling Amendment**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to a telephone conversation between Taro and the Agency on December 14, 1999 and with Dr. Christina Chi and Cheryl Turner on January 19, 2000.

We are submitting herewith 15 copies of labeling for the carton, tube and educational brochure, along with 3 diskettes which contain the text of this labeling in Word 6.0. Four of the copies of the carton label have been annotated to indicate the font size of the "Drug Facts" information on the back panel.

Please note that I have put this labeling in "final printed" format and we have used one of our proposed names (Vagizole 3) for ease of presentation. We understand that the Agency, in the event of requested revisions, and/or the selection of an alternate brand name, will request further final printed labeling.

Sincerely,  
Taro Pharmaceuticals U.S.A., Inc.

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi



February 3, 2000

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

9

54

**Re: NDA # 21-143 (Clotrimazole Vaginal Cream, 2%)  
Safety Update Report**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to phone conversations between Taro and Dr. Christina Chi.

Pursuant to 21 CFR 314.50 (d) (5) (vi) (b), we are herewith submitting a Safety Update Report that covers the time period from June 15, 1999 to the present.

Sincerely,

**Taro Pharmaceuticals U.S.A., Inc.**

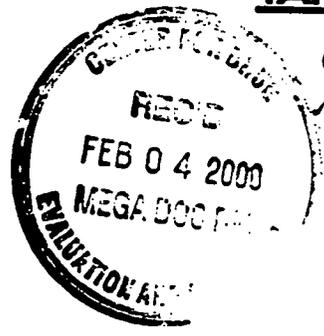
Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi

Dr. Ling Chin, Division of OTC Products



BF



February 3, 2000

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: NDA # 21-143 (Clotrimazole Vaginal Cream, 2%)  
Amendment to Labeling Amendment**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to the labeling amendment submitted on January 19, 1999. Reference is also made to recent phone conversations with Dr. Christina Chi and Cheryl Turner regarding the submitted labeling.

We are submitting herewith 21 revised copies of labeling for the carton, along with 3 diskettes which contain the text of this labeling in Word 6.0. Four of the copies of the carton label have been annotated to indicate the font size of the "Drug Facts" information on the back panel. The previously submitted tube and educational brochure labeling is not being revised at this time.

Please note that as was done with the labeling submitted on January 19, we have put this labeling in "final printed" format and we have used one of our proposed names (Vagizole 3) for ease of presentation. We understand that the Agency, in the event of requested revisions, and/or the selection of an alternate brand name, may request further final printed labeling.

Sincerely,  
**Taro Pharmaceuticals U.S.A., Inc.**

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi

DUPLICATE

NDA ORIG AMENDMENT

BC



TARO PHARMACEUTICALS INC.  
130 EAST DRIVE  
BRAMALEA, ONTARIO  
L6T 1C3

March 8, 2000

Norman R. Schmuff, Ph.D., Chemistry Team Leader  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

4



Re: Amendment to NDA  
Trivagizole-3  
(Clotrimazole Vaginal Cream, 2%)  
NDA # 21-143

Dear Dr. Schmuff,

Please find enclosed responses to your CMC comments received by fax on February 22, 2000.

Comment 1

*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), specifications for residual solvents and specifications for microbial limits.*

**Response:**

The specification for Clotrimazole, USP drug substance has been revised to include limits for single unknown impurity, total unknown impurities and total of all impurities. In addition specifications for residual solvents have been included and the results will be transcribed from supplier's certificates of analysis. A copy of the revised specification No. RK-13-01 dated March 7, 2000 is provided in Supplementary Page 04.

The microbial examination is performed on the finished packaged product and stability. Test and limits for this test have been included in the release and stability specifications.

DUPLICATE

TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-4767  
905-791-5008

**Comment 2**

*The production description ends with the filling of the holding containers. Where is the packaging (tubes filling) procedure described?*

**Response:**

The tubes filling procedure was described in the NDA Summary (page 97 of the NDA) and in the packaging documents which were provided on pages 201 – 210 of the NDA.

**Comment 3**

*The diagram on page 0188 starts with Step #3. How about Steps #1 and 2?*

**Response:**

Steps #1 and 2 are QA checks prior to actual manufacturing.

Step #1 of the manufacturing process is checking to ensure that the quantity of each raw material is sufficient and within expiry date and step #2 is verifying the appropriate sections of the pre-start operations have been completed.

**Comment 4**

*Please include another identification method, in addition to [redacted] for clotrimazole in the regulatory specifications for the drug product.*

**Response:**

A TLC test for identification has been included in the specification for the finished packaged product. A copy of the revised specification may be found in supplementary page 05.

**Comment 5**

*What is the limit of quantitation for benzyl alcohol and benzaldehyde in the new [redacted]*

**Response:**

In our [redacted] the limit of quantitation of benzyl alcohol and benzaldehyde has not been established. In accordance with USP 24 <1225>, preservative assay is a category 1 test and does not require either a detection or quantitation limit.

TARO PHARMACEUTICAL  
TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-5008

**Comment 6**

*Please provide any available data from the applicator dosage evaluation studies.*

**Response:**

Data from applicator dosage evaluation studies is provided in Supplementary Page 07.

**Comment 7.**

*Please include a specification for each degradation product and total degradation products in the regulatory specifications for the drug product.*

**Response:**

The regulatory/release specification provided in supplementary page 05 has been revised to include limits for each degradation product and total degradation products. The stability specifications have also been revised and are provided in supplementary pages 08 - 09.

**Comment 8.**

*Please reconcile the regulatory specifications listed on page 0299 (section 2.6, vol. 1.2) with the specifications and limits used in the stability studies (for example, limits for impurities, limit for pH, etc.) of the drug product (see page 0320, section 2.7, vol. 1.2).*

**Response:**

The degradation products limit on the regulatory/release specifications and the pH limits on the bulk product specifications are tighter than the stability limits.

Based on stability data compiled to date, Taro has established wider stability limits for the (o-chlorophenyldiphenyl)methanol (degradant) and the pH.

The release and in-process bulk specifications were provided in supplementary pages 05 - 06.

**TARO PHARMACEUTICALS**  
TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-5008

**Comment 9.**

*Please provide the results of viscosity testing in the stability studies of the cream packaged in the commercial tubes (for batches 7B211, 7C321 and 8F018).*

**Response:**

Updated stability summaries which include results of viscosity testing for batch No. 7B211 (36 months) and 8F018 (18 months) are provided in supplementary pages 10 - 13. Viscosity testing of Batch No. 7C321 is not available. This test will be performed in the upcoming time point (36-month testing, due in March 2000) and results will be forwarded to the agency when they become available.

**Comment 10.**

*Please provide any available results from the stability testing of the cream performed at conditions other than room temperature [redacted] conditions. Please provide any available, beyond 9 months, room temperature [redacted] testing results for the batch.*

**Response:**

Updated room temperature stability data [redacted]  
[redacted] have been provided in supplementary pages 09 - 13.

[redacted]

Results of stability testing of Clotrimazole Vaginal Cream, 2% performed at conditions other than room temperature are not available.

**Comment 11.**

*Please provide the applicable CFR reference, on which Taro Inc. claims a categorical exclusion from the EA requirement for clotrimazole, vaginal cream, 2%.*

**Response:**

Taro claims a categorical exclusion for the EA requirement for Clotrimazole Vaginal Cream, 2% in accordance with CFR 21 §25.31(a). A copy of the applicable page from the CFR 21 is provided in supplementary page 14.

TARO PHARMACEUTICAL  
TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-5008

*In the amendment addressing the above we remind you of the February 9, 2000 telephone conversation between Lorraine Sachs of Taro and Norman Schmuff, Chemistry Team Leader, HFD-590, in which you indicated that you would withdraw the two alternate testing facilities not listed in your submission of July 16, 1999.*

At the Agency's request, we are herewith withdrawing the two alternate testing facilities, [redacted] without prejudice to future filings (post approval of the NDA).

This completes Taro's response to the comments listed above. If there are any further questions, please feel free to contact us at:

Taro Pharmaceuticals USA, Inc.  
Attn: Lorraine W. Sachs, RAC  
Associate Director Regulatory Affairs  
5 Skyline Drive  
Hawthorne, NY 10532  
Tel: (914) 345-9001 ext. 282.

Sincerely,  
Taro Pharmaceuticals Inc.



Derek Ganes, Ph.D.  
VP, Regulatory Affairs

L. Ogbaghebiel

TARO PHARMACEUTICAL  
TELEPHONE  
905-791-8276  
1-800-268-1975  
VOICE MAIL  
905-791-5181  
TELEFAX NO.  
905-791-5008



March 17, 2000

Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: NDA # 21-143**  
**Trivagizole 3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%)**  
**Labeling Amendment**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to a facsimile containing the Agency's labeling comments dated March 16, 2000.

We are submitting herewith 2 copies of the current draft labeling for the carton, tube and educational brochure. We are also submitting, under separate cover, nineteen copies of this package as personal desk copies for use by Dr. Christina Chi.

We are also submitting copies of the script used for the recording of our 24 hour automated information line referred to in our carton label. Please note that since this is the same phone line used for Taro's Clotrimazole Vaginal Cream, 2 % marketed as a private label product under Schering's NDA 20-574 for Gyne-Lotrimin 3 ®, we refer to the product by it's generic name. "Clotrimazole Three-Day Cream," and not by Trivagizole 3. Since this product is currently being launched, the 24 hour automated line will be available to consumers by the week of March 20, 2000.

Sincerely,  
**Taro Pharmaceuticals U.S.A., Inc.**

A handwritten signature in cursive script, appearing to read "Lorraine W. Sachs".

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi

March 20, 2000



Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re:           NDA # 21-143**  
**Trivagizole 3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%)**  
**General Correspondence**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to a phone conversation between Lorraine Sachs of Taro and Dr. Christina Chi of the Agency on March 16, 2000.

At this time we would like to address the following issues prior to the approval of our application.

1. **Change of Ownership from Taro Pharmaceuticals Inc., Bramalea, Ontario, Canada to Taro Pharmaceuticals U.S.A., Inc., Hawthorne, New York, U.S.A.**

The ownership of this NDA is being officially transferred to:

Taro Pharmaceuticals U.S.A., Inc.  
5 Skyline Drive  
Hawthorne, N.Y., U.S.A. 10532

Responsible Official: Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

As is required in 21 CFR § 314.72, we are herewith submitting the following information in support of this change of ownership:

- A letter signed by a corporate director of the former owner, Taro Pharmaceuticals Inc., which states that all rights to the application have been transferred to Taro Pharmaceuticals U.S.A., Inc.
- A Form FDA 356(h) for the application indicating the new owner and signed by the Responsible Official.

- We hereby commit to all agreements, promises and conditions made by the former owner, Taro Pharmaceuticals Inc.
- The change of ownership is effective as of today, March 20, 2000.
- We certify that we have a complete copy of the approved application, including all amendments, at 5 Skyline Drive, Hawthorne, N.Y., U.S.A.
- Please note that since the product will continue to be manufactured by Taro Pharmaceuticals Inc. in Bramalea, Ontario, Canada and distributed by Taro Pharmaceuticals U.S.A., Inc. in Hawthorne, N.Y., U.S.A., no changes due to the change of ownership will be made to the product labeling.
- We hereby commit to inform FDA regarding all future changes to the application required under 21 CFR § 314.70.

2. **Pediatric Studies**

We wish to inform the agency that we have not conducted pediatric studies for this drug product and we do not intend to pursue a pediatric indication for this vaginal product intended for administration to women over the age of 12.

3. **Initial Marketing Campaign**

Please note that we are not planning an initial marketing campaign for this product under this NDA and we are therefore not making a pre-approval submission to DDMAC at this time.

Sincerely,  
Taro Pharmaceuticals U.S.A., Inc.



Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi



TARO PHARMACEUTICALS INC.  
130 EAST DRIVE  
BRAMALEA, ONTARIO  
L6T 1C3

March 20, 2000

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room, MPN II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Re: **NDA #21-143**  
**Trivagizole 3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%)**

Dear Sir/Madam:

Reference is made to the above unapproved NDA.

We wish to inform you that as of today's date, we are officially transferring ownership of these ANDA's to:

Taro Pharmaceuticals, U.S.A., Inc.  
5 Skyline Drive  
Hawthorne, NY 10532

Responsible Official: Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

Sincerely,

*Alexander Cossin*  
Alexander Cossin, ESQ.  
Secretary, Taro Pharmaceuticals Inc.

March 22, 2000



Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re:           NDA # 21-143**  
**Trivagizole 3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%)**  
**Labeling Amendment**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA labeling comments dated March 16, 2000.

We are submitting herewith 2 copies of the current draft labeling for the carton, tube and educational brochure. We are also submitting, under separate cover, twenty sets of copies of this labeling as personal desk copies for use by Dr. Christina Chi. We are also sending individual sets of copies to Leah Palmer of DDMAC, William Nychis of the Office of Compliance, and Patrick Guinn of OPDRA.

Should you have any questions or comments, please do not hesitate to contact me at (914) 345-9001, ext. 282. Thank you for your attention in this matter.

Sincerely,  
**Taro Pharmaceuticals U.S.A., Inc.**

A handwritten signature in black ink, appearing to read "Lorraine W. Sachs".

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

cc: Dr. Christina Chi  
Leah Palmer  
William Nychis  
Patrick Guinn



March 31, 2000

Norman R. Schmuff, Ph.D., Chemistry Team Leader  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: Amendment to NDA  
Trivagizole-3<sup>TM</sup>  
(Clotrimazole Vaginal Cream, 2%)  
NDA # 21-143**

Dear Dr. Schmuff,

Reference is made to our New Drug Application for Trivagizole-3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%) and to a telephone conference of March 21, 2000, between Taro Pharmaceuticals Inc. and the Agency's personnel, including yourself, Dr. Christina Chi and Dorota Matecka in which the comments outlined below were made.

Taro Pharmaceuticals Inc. is hereby submitting an amendment addressing the issues raised during the teleconference and the necessary revised documentation and batch analysis data. For ease of review, your comments have been summarized and presented in a question and answer format.

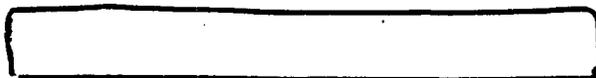
**Comment 1**

*With respect to the active drug substance, please provide batch analysis data in tabular form to support your proposed specification for impurities and residual solvents. Also establish limits for residual solvents*

**Response:**

Batch analysis data of 13 batches of the drug substance, Clotrimazole, USP, have been tabulated and are provided in Supplementary Page 1. The results presented support our proposed specifications for impurities and residual solvents.

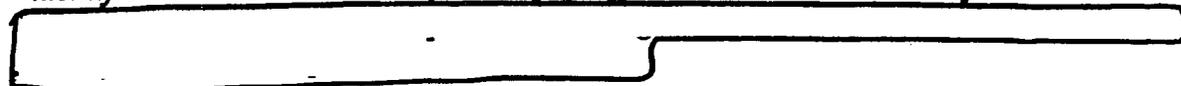
The drug substance specification has been revised to establish limits for residual solvents as follows:



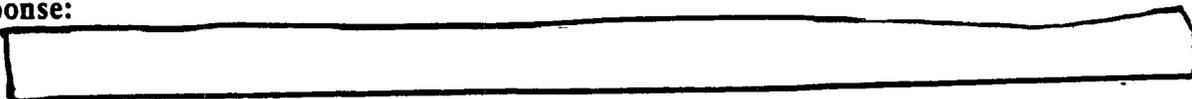
A copy of the revised specification sheet is provided in **Supplementary Page 2**.

**Comment 2**

*With respect to Identification test on the finished product, two chromatographic identification tests will be accepted only if different methods were used for each test.*



**Response:**



**Comment 3**

*The data submitted for Applicator Dosage Evaluation Studies gave an average result of [ ] per applicatorful. Evaluate other applicator batches and submit results. In addition, since the applicator are reusable, fill, wash and dry and evaluate the applicators three times to simulate actual use.*

**Response:**

Ten reusable applicators from one additional batch have been evaluated in accordance with your recommendations. The results are provided in **Supplementary Page 3**.

**Comment 4**

*Please designate the revised stability specifications to indicate that they are "Regulatory" specifications.*

**Response:**

As recommended, Taro's stability specifications have been designated as the "Regulatory Specifications". A copy of this specification is provided in **Supplementary Page 4**.

**Comment 5**

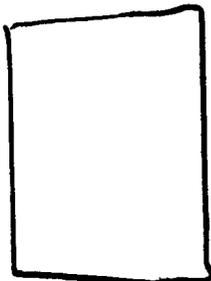
***Concerning the specifications for release and stability:***

- a. ***The data previously submitted would only support a limit for Related Compound A of [ ] Please submit additional data that would be supportive of your proposed limit of [ ]***
- b. ***The proposed pH range [ ] is too wide. Please propose a narrower range.***

**Response:**

- a. Based on stability data compiled to date, the stability limits for degradation products have been tightened and are included in the Regulatory Specification which was provided in Supplementary Pages 4:

Related Compound A:  
Imidazole:  
Benzophenone:  
Chlorobenzophenone:  
Individual Unknown:  
Total:



- b. As recommended, we have established a tighter range for pH [ ] and revised the regulatory specifications accordingly.

**Comment 6**

***With respect to viscosity testing on stability, results for future testing stations must be reported in annual reports (post-approval). In addition, after sufficient data on viscosity has been obtained, the viscosity limits may be revised post-approval as warranted.***

**Response:**

Viscosity results of the on-going stability studies for future testing stations and results of post-approval marketed batches will be submitted in our annual reports post-approval.

We acknowledge your recommendations with regard to viscosity limits and we commit to revise the limits post-approval if the data does not justify our currently proposed limits.

This completes Taro's response to the comments listed above. If there are any further questions, please feel free to contact us at:

Taro Pharmaceuticals USA, Inc.  
Attn: Lorraine W. Sachs, RAC  
Associate Director Regulatory Affairs  
5 Skyline Drive  
Hawthorne, NY 10532  
Tel: (914) 345-9001 ext. 282.

Sincerely,  
Taro Pharmaceuticals Inc.



Derek Ganes, Ph.D.  
VP, Regulatory Affairs

/L. Ogbaghebriel

APPEARS THIS WAY  
ON ORIGINAL

April 3, 2000



Mark Goldberger, M.D., Director  
Office of Drug Evaluation IV  
Div. of Special Pathogens and Immunologics Drug Products, HFD-590  
Central Document Room  
Food and Drug Administration  
9201 Corporate Boulevard  
Rockville, M.D. 20850

**Re: NDA # 21-143**  
**Trivagizole 3<sup>TM</sup> (Clotrimazole Vaginal Cream, 2%)**  
**General Correspondence**

Dear Dr. Goldberger:

Reference is made to our unapproved NDA and to a phone conversation between Lorraine Sachs of Taro and Dr. Christina Chi of the Agency on March 23, 2000.

At this time we are requesting a full waiver of the requirement to provide data in support of a pediatric use indication as per 21 CFR § 314.55 (c). Accordingly, we are hereby certifying to the following:

1. The drug product which is the subject of NDA 21-143, Trivagizole 3<sup>TM</sup>, does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. It is our estimate that less than 50,000 pediatric patients between the ages of 0 to 12 years would be able to benefit from the use of this drug product.
2. Because of the small number of pediatric patients that would be available, the necessary studies are impossible or highly impractical to conduct.

Should you have any questions or comments, please do not hesitate to contact me at (914) 345-9001, ext. 282. Thank you for your attention in this matter.

Sincerely,  
**Taro Pharmaceuticals U.S.A., Inc.**

A handwritten signature in black ink, appearing to read "Lorraine W. Sachs".

Lorraine W. Sachs, RAC  
Associate Director, Regulatory Affairs

**cc:** Dr. Christina Chi