CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-143

ADMINISTRATIVE DOCUMENTS

D. Patent Information

Patent Information

According to the information obtained from the Electronic Orange Book (May 27, 1999), there are no unexpired patents for this product.

Market exclusivity No. 020574, Exp. Nov. 24, 2001 was granted to Schering-Plough HealthCare Products (SPHCP). SPHCP waives this exclusivity specifically to Taro Pharmaceuticals Inc. A copy of a letter from SPHCP is provided on the following page.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

020574	001	NP	NOV 24,2001

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

EXCLUSIVITY SUMMARY for NDA # 21-143 **SUPPL #** /

Trade Name Trivagizole 3™ Vaginal Cream **Generic Name** clotrimazole vaginal cream 2%

Applicant Name Taro Pharmaceuticals, Inc. **HFD-** 590

Approval Date April 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /✓/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /✓/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /✓/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      It is not a bioavailability study which is needed; only safety review is done.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /✓/ NO /___/

If yes, NDA # 20-571 Drug Name Cyproheptadine 3[e]

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 3/20/2000

Signature of Preparer Date

Title: Project Manager (Reg. Health Reg Coordinator)

/S/ 4/13/00

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last a ction.

NDA/~~PLA/EMA~~# 21-143 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510 Trade and generic names/dosage form: Trivagizole 3™ Vaginal Cream (clotrimazole vaginal cream) 2% Action (AP) AE NA

Applicant Taro Pharmaceuticals USA, Inc. Therapeutic Class Vaginal antifungal

Indication(s) previously approved (Vaginal Antifungal) for Candidiasis 3 day therapy

Pediatric information in labeling of approved indication(s) is adequate __inadequate __ None, N/A.

Proposed indication in this application 3 day therapy for Vaginal Candidiasis

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) __ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) ✓Adolescents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

✓ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply**, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from: (memo) (e.g., medical review, medical officer, team leader).

Signature of Preparer and Title CSO

March 29, 2000
Date

cc: Archival NDA/~~PLA/EMA~~# 21-143
HFD-510/Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)

DEBARMENT CERTIFICATION

Taro Pharmaceuticals Inc. hereby certifies that, to the best of its knowledge, it has not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act, in connection with this application. In addition, to the best of its knowledge, Taro Pharmaceuticals Inc. states that neither Taro Pharmaceuticals Inc. nor any individuals, partnerships, corporations, or associations responsible for the development or submission of this application have been convicted as described in Section 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act.

Taro Pharmaceuticals Inc.

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

June 8, 1999
Date

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21143/000
Stamp: 17-JUN-1999
Regulatory Due: 17-APR-2000
Applicant: TARO PHARMS (CA)
5 SKYLINE DR
HAWTHORNE, NY 10532
Priority: 3S
Org Code: 590

Action Goal:
District Goal: 17-FEB-2000
Brand Name: CLOTRIMAZOLE 2% CREAM
Estab. Name:
Generic Name: CLOTRIMAZOLE 2% CREAM

Dosage Form: (CREAM)
Strength: 2%

Application Comment: THIS IS A NEW NDA FOR CLOTRIMAZOLE VAGINAL CREAM, 2%. (on 02-AUG-1999 by D. MATECKA (HFD-590) 301-827-2398)

FDA Contacts:

C. CHI	(HFD-590)	301-827-2166	, Project Manager
D. MATECKA	(HFD-590)	301-827-2398	, Review Chemist
N. SCHMUFF	(HFD-590)	301-827-2425	, Team Leader

Overall Recommendation: ACCEPTABLE on 20-MAR-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: CSN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-1999				MATECKAD
SUBMITTED TO DO	04-AUG-1999	GMP			ADAMSS
ASSIGNED INSPECTION	06-AUG-1999	GMP			EGASM
INSPECTION SCHEDULED	23-NOV-1999		28-JAN-2000		IRIVERA
INSPECTION PERFORMED	01-FEB-2000		27-JAN-2000		EGASM
DO RECOMMENDATION	20-MAR-2000			ACCEPTABLE	EGASM
OC RECCMMENDATION	20-MAR-2000			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9614240
TARO PHARMACEUTICALS INC
L6T 1C3
BRAMALEA, ONTARIO, CA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: OIN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-1999				MATECKAD
OC RECOMMENDATION	04-AUG-1999			ACCEPTABLE BASED ON PROFILE	ADAMSS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
TARO PHARMACEUTICALS INC.

DATE OF SUBMISSION
07/16/99

TELEPHONE NO *(Include Area Code)*
905-791-8276

FACSIMILE (FAX) Number *(Include Area Code)*
905-791-5008

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
TARO PHARMACEUTICALS U.S.A., INC.
5 SKYLINE DRIVE
HAWTHORNE, NY 10532
PHONE: (914) 345-9001 FAX: 914-345-8728

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-143

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
CLOTRIMAZOLE VAGINAL CREAM USP, 2%

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
1-(O-CHLORO- -DIPHENYLBENZYL) IMIDAZOLE

CODE NAME *(If any)*

DOSAGE FORM: CREAM

STRENGTHS: 2%

ROUTE OF ADMINISTRATION: VAGINAL

(PROPOSED) INDICATION(S) FOR USE: ANTIFUNGAL AGENT IN THE MANAGEMENT OF DERMAL INFECTIONS

APPLICATION INFORMATION

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

IF AN NDA IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA OR AADA IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug
Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION AMENDMENT

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

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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

MANUFACTURING/PACKAGING/CONTROLS: TARO PHARMACEUTICALS INC., 130 EAST DRIVE, BRAMALEA, ONTARIO L6T 1C3 (ESTABLISHMENT #61360)

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

NDA #20-574 - SCHERING-PLOUGH'S GYNE-LOTRIMIN 3

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

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

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

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

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

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE KALPANA RAO ASSOCIATE DIRECTOR, REGULATORY AFFAIRS	DATE 7/16/99
ADDRESS *(Street, City, State, and ZIP Code)* 5 SKYLINE DRIVE, HAWTHORNE, NY 10532		Telephone Number ((914) 345-9001

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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

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

Form Approved : OMB No. 0910-0338
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APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
TARO PHARMACEUTICALS INC.	01/05/00
TELEPHONE NO *(Include Area Code)* 905-791-8276	FACSIMILE (FAX) Number *(Include Area Code)* 905-791-5008

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
TARO PHARMACEUTICALS U.S.A., INC.
5 SKYLINE DRIVE
HAWTHORNE, NY 10532
PHONE: (914) 345-9001 FAX: 914-593-0078

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-143

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
CLOTRIMAZOLE VAGINAL CREAM USP, 2%	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
1-(O-CHLORO-α,α-DIPHENYLBENZYL) IMIDAZOLE

CODE NAME *(If any)*

DOSAGE FORM: CREAM	STRENGTHS: 2%	ROUTE OF ADMINISTRATION: VAGINAL

(PROPOSED) INDICATION(S) FOR USE: ANTIFUNGAL AGENT IN THE MANAGEMENT OF DERMAL INFECTIONS

APPLICATION INFORMATION

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

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

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Gyne-Lotrimin 3 3-Day Vaginal Cream Holder of Approved Application: Schering-Plough Corporation

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Amendment - Suggested Names

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

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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

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

This application contains the following items: *(Check all that apply)*	
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	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
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	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FDA&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Amendment - Suggested Names

CERTIFICATION

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

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

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

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

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE LORRAINE W. SACHS, RAC ASSOCIATE DIRECTOR, REGULATORY AFFAIRS	DATE 1/5/00
ADDRESS *(Street, City, State, and ZIP Code)* 5 SKYLINE DRIVE, HAWTHORNE, NY 10532		Telephone Number ((914) 345-9001

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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

FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
TARO PHARMACEUTICALS INC.

DATE OF SUBMISSION
03/17/00

TELEPHONE NO. *(Include Area Code)*
905-791-8276

FACSIMILE (FAX) Number *(Include Area Code)*
905-791-5008

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
TARO PHARMACEUTICALS U.S.A., INC.
5 SKYLINE DRIVE
HAWTHORNE, NY 10532
PHONE: (914) 345-9001 FAX: 914-593-0078

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-143

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
CLOTRIMAZOLE VAGINAL CREAM USP, 2%

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
1-(O-CHLORO- -DIPHENYLBENZYL) IMIDAZOLE

CODE NAME *(if any)*

DOSAGE FORM: CREAM

STRENGTHS: 2%

ROUTE OF ADMINISTRATION: VAGINAL

(PROPOSED) INDICATION(S) FOR USE: ANTIFUNGAL AGENT IN THE MANAGEMENT OF DERMAL INFECTIONS.

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Name of Drug Gyne-Lotrimin 3 3-Day Vaginal Cream Holder of Approved Application Schering-Plough Corporation

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Labeling Amendment of March 16, 2000.

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

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE LORRAINE W. SACHS, RAC ASSOCIATE DIRECTOR, REGULATORY AFFAIRS	DATE 3/17/00
ADDRESS *(Street, City, State, and ZIP Code)* 5 SKYLINE DRIVE, HAWTHORNE, NY 10532		Telephone Number ((914) 345-9001

Safety Update Report
21 CFR – 314.50 (d) (5) (vi) (b)

As indicated in the Original submission, Taro Pharmaceuticals Inc. markets Clotrimazole Vaginal Cream in 1% and 2% formulations in Canada and in a 1% formulation in the United States.

Since the last submission of the safety report, Taro did not receive any ADR's on any of the formulations either in Canada or in U.S.A. Therefore, Taro Pharmaceuticals Inc. does not have any additional or new safety information to report in Clotrimazole Vaginal Cream, 2% NDA# 21-143.

Safety Update Report
June 15, 1999 – February 3, 2000

During this time period, Taro Pharmaceuticals Inc. has not received any reports of adverse reactions for either the Clotrimazole Vaginal Cream 1% formulation marketed in both the U.S.A. and Canada; or the 2% formulation marketed in Canada. However, Schering-Plough Corporation has provided us with Medwatch forms for the following eight ADR's received by them their under NDA 20-574 for Gyne-Lotrimin 3® Vaginal Cream during this time period. These ADR's are summarized as follows:

Non-Serious Unlabeled (2)

Manufacturer Control Number	Drug Experience Terms
1. 1999-06-0172	Condition Aggravated
2. 1999-10-1477	Trauma

Non-Serious Labeled (6)

Manufacturer Control Number	Drug Experience Terms
1. 1999-07-0686	Therapeutic Response Decrease
2. 1999-10-1415	Therapeutic Response Decrease
3. 1999-10-1487	Therapeutic Response Decrease
4. 1999-11-0421	Therapeutic Response Decrease
5. 1999-11-0943	Therapeutic Response Decrease
6. 1999-11-1017	Therapeutic Response Decrease

Attached please find complete copies of the applicable Medwatch forms. Schering-Plough has requested that both Taro Pharmaceuticals and the Agency hold this information as confidential in relation to their NDA 20-574 for Gyne-Lotrimin 3® Vaginal Cream.

April 9, 1997

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

RE: REQUEST FOR A MEETING

Dear Dr. Chi,

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

Purpose

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

Specific Objectives

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

Agenda:

1) Brief review of the clinical and mycological result of both studies (15 min.).

2) Brief review of the two formulations utilized in the clinical studies (10 min.).

3) In vitro release data (10 min.).

4) Discussion of the specifics of compiling an NDA using Schering and Taro studies (25 min.).

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

Attendees from Schering and Taro

Schering Plough
Joe Clark, Ph.D.
John Clayton, Ph.D.

Taro Pharmaceuticals U.S.A., Inc.
Dan Moros, M.D.
Avraham Yacobi, Ph.D.
Terry Feldman, Ph.D.

Requested Participants from CDER:
Dr. David Feigal
Dr. Christina Chi
Dr. Renata Albrecht
Dr. Joseph Winfield
Dr. Eric Sheinin

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

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

With many thanks for your effort.

Sincerely,

A. Yacobi

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

cc: Joe Clark, Ph.D.

June 4, 1997

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

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

Dear Dr. Chi:

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

The attendees from each company will be as follows:

Schering-Plough

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

Taro Pharmaceuticals U.S.A. , Inc.

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

The agenda for the meeting will be as follows:

1. Introduction and objectives of the Taro-Schering-FDA meeting (Dr. Moros, 5 minutes)

2. Brief review of the two formulations utilized in the clinical studies and the in-vitro release data (Dr. Feldman, 5 minutes)

3. Protocol design comparison of Schering and Taro studies (Dr. Clark, 5 minutes)

4. Brief review of clinical and mycological results of Schering study (Dr. Clark, 5 minutes)

5. Brief review of the clinical and mycological results of both studies (Dr. Moros, 5 minutes)

6. Discussion of the specifics of compiling an NDA using Schering and Taro studies (Dr. Clayton, 5 minutes)

7. Summary of Schering/Taro proposals (Dr. Moros, 5 minutes)

8. Question and answer period (Taro-Schering-FDA, 30 minutes)

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

Sincerely,

A. Yacobi

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

PRE-NDA MEETING
TARO & SCHERING-PLOUGH

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 18, 1997

Time: 11:30 AM - 1:00 PM

Location: 9201 Corporate Blvd., Rockville, MD 20850

Application: Taro: Pre-NDA Clotrimazole 2% Vaginal Cream (No IND)
Schering: NDA 20-574 GyneLotrimin 3, Clotrimazole 2% Cream

Type of Meeting: Pre-NDA meeting; possibility of an NDA joint submission between the two companies for a product which is going to be marketed OTC.

Meeting Chair & Recorder: Christina H. Chi, Ph.D., Project Manager

FDA Attendees:

Division of Over The Counter Drug Products:
Linda Katz, M.D., M.P.H., Deputy Division Director
Helen Cothran, Team Leader
Sakineh Walther, R.N., Project Manager

Division of Special Pathogens And Immunologic Drug Products:
Mark Goldberger, M.D., Acting Division Director
Renata Albrecht, M.D. Deputy Division Director
Christina Chi, Ph.D., Project Manager
Philip Colangelo, Ph.D., Biopharmaceutics Reviewer
Daniel Davis, M.D., Medical Officer
Carmen DeBellas, Acting Supervisor Regulatory Health Manager
Linda Gosey, Microbiologist
Sheryl Lard, Ph.D., Acting Microbiology Team Leader
Brad Leissa, M.D., Medical Team Leader
Dorota Matecka, Ph.D., Chemistry Reviewer
Owen McMaster, Ph.D., Pharmacology Reviewer
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader
Norman Schmuff, Ph.D., Chemistry Acting Team Leader
Nancy Silliman, Ph.D., Acting Supervisor Statistician
Joseph Winfield, M.D., Medical Officer

Office of Generic Drug:
Donald Hare, Special Assistant to the Director

PRE-NDA MEETING
TARO & SCHERING-PLOUGH

Sponsor Attendees: **Taro Pharmaceuticals, USA, INC.**
Avraham Yacobi, Ph.D., Chief E.O. President.
Daniel Moros, M.D., Vice Chairman, Med. Dir.
Terry Feldman, Ph.D., V.P., Res. & Development.

Schering-Plough HealthCare Products
Joseph Clark, Ph.D., V.P., Reg. Affairs
Mary Williams, Assoc. Dir, Reg. Affairs

Background:

April 27, 1995: Schering-Plough submitted NDA 20-574 for GyneLotrimin 3 (clotrimazole) Vaginal Cream 2%. This was a 3-day therapy for vaginal yeast infections (candidiasis). Both had 3-arm studies, comparing the 3-day to the 7-day treatments and the 1-day to the 7-day treatments. The results indicated that the 7-day 1% was equivalent to the 3-day 2% cream in one study. In the other study, the 7-day 1% was equivalent to the 3-day 1%. Because two studies were required, the data submitted did not support approval for either the 1-day or the 3-day as equivalent to the 7-day product.

January 29, 1996: The applicant chose to withdraw the application.

September 12, 1996: The Agency met with Taro to discuss evaluability criteria and clinical trial design for a proposed clotrimazole 2% vaginal cream for a one or three day therapy to treat vaginal yeast infections (Candidiasis). Based on this meeting, it was concluded that this study would support the 3-day treatment, because efficacy was generally better in the 3-day treatment group (vs. the 1-day arm).

January 10, 1997: Schering-Plough and Taro entered into a joint venture (based on an earlier business agreement of October 22, 1993, between Schering-Plough and Taro) for both parties to provide data needed to support the approval of a 3-day clotrimazole 2% vaginal cream.

Meeting Objectives:

1. To seek FDA's comment on their pooling the data from two clinical trials done by Schering-Plough into one study.

2. To seek FDA's comment on the use of Taro's data with their 3-day 2% vaginal cream as the second study to support Schering's direct-OTC NDA.

3. To seek the reactivation of Schering's NDA with Schering as the manufacturer and Taro as the distributor.

Discussion points and agreements reached:

1. The FDA agreed that it appears reasonable to pool the two Schering clinical studies (93-34 and 93-40) as a single study.

2. The FDA suggests that the pooled data from these two studies be reanalyzed using the FDA's current evaluability criteria.

3. Pending the results of Taro's study (95-50 – an on-going study), a determination will be made as to whether the pooled study from Schering can be used in conjunction with Taro's study to support approval of Schering's NDA.

4. The FDA cannot assume that the two different formulations have identical activity. The sponsors must demonstrate that the activity of the two different products are the same (do a clinical study of 2 arms to bridge the difference). Therefore, the FDA recommended that the two companies perform a "bridging" study demonstrating therapeutic equivalence between their respective formulations of the two products.

5. The FDA will not accept *in-vitro* data alone as the "bridging" study.

6. Linda Katz, OTC, stated that over 5 years of marketing experience is desired for a product to receive direct OTC marketing approval.

7. Taro has a 3-day 2% cream currently marketed in Canada (over 5 years since approval) while Schering doesn't have this experience with their product. The FDA has difficulty extrapolating Taro's safety experience to support Schering's product, because the formulations are different. In light of Taro's postmarketing experience, it may be easier for Schering's data to support Taro's product – rather than the reverse.

Unresolved issues or issues requiring further discussion:

1. The sponsors will consider a new clinical study to bridge the two formulations. They

stated that they will provide the FDA with a response on this issue within 1-2 weeks.

2. If the sponsors do not want to conduct a bridging study, they may request that FDA seek General Counsel's opinion on whether the data from two different formulations can be used (with no direct comparison between the two) to support approval.

3. The sponsors will decide which of the two formulations (Schering's or Taro's) to market.

Projected submission date: uncertain at this time.

Action Items: None.

/S/

Minutes Preparer: Christina Chi, Ph.D. 7/2/97

Chair Concurrence: Carmen DeBellas 6/20/'97

Attachments:

meeting request:	2 pages
pre-meeting package:	10 pages
meeting transparencies:	2 pages
summary of NDA 20-574 clinical studies:	1 page
Total:	15 pages

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

July 8, 1997

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

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

Dear Dr. Chi:

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

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

Sincerely,

Mary E. Williams
Associate Director
Regulatory Affairs

attachment

To Distribution

From Mary Williams MW

Date 7/8/97

Subject **Minutes of 6/18/97 FDA Meeting on Clotrimazole 2% Cream NDA**

On June 18, 1997 representatives from the FDA, Schering-Plough HealthCare Products (SPHCP) and Taro Pharmaceuticals (see Attachment 1 for list of attendees) met at the FDA Corporate Boulevard facility to discuss the proposed joint strategy for a 2% clotrimazole cream NDA. (See Attachment 2 for overheads.)

PROPOSAL AND RATIONALE

Dr. Daniel Moros (Taro) opened the discussion with a brief history on the use of antifungals to treat vaginal yeast infections, including a list of the critical studies SPHCP and Taro have conducted to demonstrate bioequivalence of various dosing regimens of clotrimazole to the 1% / 7 day "gold standard". Noting that SPHCP and Taro each have one pivotal study which supports a 2% / 3-day cream product, Dr. Moros informed the group that SPHCP and Taro would like to combine their work and jointly pursue approval of a single NDA. The purpose of this meeting was to outline the strategy and gain FDA feedback on the proposal.

Dr. Joseph Clark (SPHCP) then reviewed SPHCP's history of 3-day vaginal yeast products, i.e., insert, combination pack, and cream. Early in his review of the data for the pending 3-day cream NDA, Dr. Winfield (FDA Medical Officer) had concluded that one of the pivotal studies supported the 2% / 3-day treatment while the other pivotal study supported a 1% / 3-day treatment, resulting in the need for an additional study. This led SPHCP to withdraw the 3-day cream NDA (1/26/96) so that the FDA could focus their attention on the insert and combination pack pending NDAs (subsequently approved 7/29/96). At SPHCP's request, a meeting was held with the FDA on April 4, 1996 where agreement was reached on revised pass/ fail criteria for a future cream study and on the decision that only the 2% clotrimazole cream should be pursued for direct OTC marketing.

Since that meeting, SPHCP and Taro have decided to explore joint development of a 2% clotrimazole cream NDA, but are seeking the Agency's counsel before preceding. Specifically, guidance is requested on whether or not the data from SPHCP's two

studies are "poolable", and whether or not (given the minor differences in formulation excipients) SPHCP and Taro can combine their two studies as the pivotal clinical trials in support of a single NDA. Assuming this proposal is acceptable to the Agency, the strategy would be for SPHCP to reactivate its withdrawn NDA, amend it with a re-analysis of the SPHCP combined data using the revised criteria, and add Taro's clinical study as the second pivotal study. SPHCP would manufacture the product using its formula and include Taro in the NDA as a distributor.

Dr. Terry Feldman (Taro) presented a detailed comparison of the formulas used in SPHCP's and Taro's clinical studies which are qualitatively and quantitatively very similar. To demonstrate formula equivalence and support the use of these two formulas for a single NDA (which will seek approval of only one formula), in-vitro studies were conducted to compare the release rates of both formulas. A summary of the data was presented which demonstrated that the release rates are essentially the same for the two formulas.

Dr. Clark then gave an overview of the clinical protocols used in both SPHCP's and Taro's studies. Since both protocols were based on the FDA's guidelines, they were also essentially the same.

Finally, Dr. Clark and Dr. Moros each presented a brief review of the clinical and mycological results for their respective company's clinical studies.

QUESTION AND ANSWER PERIOD HIGHLIGHTS

- Dr. Winfield suggested that the same statistical and evaluation criteria be applied to the Taro study as that used in the SPHCP study analysis.

- Drs. Winfield and Albrecht asked if any studies had been done to demonstrate bioequivalency of the two formulas. Dr. Moros said that they had not but that both formulas had been tested against the same standard. Dr. Albrecht responded that just because A=B and C=B, that is no guarantee that A=C. In addition the FDA felt that in-vitro data by itself is not sufficient to demonstrate equivalency. When Dr. Clark pointed out that a product could go through several formulations during its development phase, Dr. Albrecht responded that this is true for oral dosage forms which are then subjected to a bioavailability study to tie all the formulations together. The outcome of this discussion was that the FDA wants a bridging study to allow the use of two different formulas to support one formula for an NDA.

- Dr. Katz advised that the OTC division's position would be that the Taro formula which is currently marketed OTC in Canada would be the preferred OTC product since it could provide an OTC safety data base. She further noted that if the SPHCP formula were used it might need to be marketed first as an Rx product. There was a brief discussion of how we might satisfy the Agency's safety concerns with the SPHCP product since it's active ingredient is the same as Taro's and it's vehicle is the same as that which has been marketed by SPHCP, both Rx and OTC, for many years with an excellent safety experience among millions of consumers.

- There was no foreseeable problem with SPHCP pooling their two clinical studies into one pivotal study for purpose of the proposed NDA.

- Dr. Albrecht indicated that if the bridging study was begun and was progressing adequately, they may begin their review of the resubmitted NDA to try to meet a six month deadline for an action. They would try to work with us to accelerate the review.

NDA 20-574

MEMORANDUM OF TELECON

DATE: September 29, 1997

APPLICATION NUMBER: NDA 20-574 clotrimazole 2% cream

BETWEEN SPONSOR:

Schering-Plough HealthCare Products:
Ronald J. Garutti, M.D., Vice President, Clinical Research/Regulatory Affairs
Walt Chambliss, Ph.D., Vice President, Research & Development
Joseph Clark, Ph.D., Consultant
Mary Williams, Associate Director, Regulatory Affairs

Taro Pharmaceuticals, USA, Inc.
Daniel Moros, M.D., Vice Chairman, Medical Director
Lorraine Sachs, RAC, Senior Regulatory Affairs Scientist

Taro Pharmaceuticals, CANADA, Inc.
Terry Feldman, Ph.D., V.P., Research & Development.

AND FDA:

Division of Over the Counter Drug Products, HFD-560:
Ling Chin, M.D., Medical Officer
Helen Cothran, Team Leader
Cheryl Turner, R.N., Interdisciplinary Scientist
Sakineh Walther, R.N., Project Manager

Division of Special Pathogens and Immunologic Drug Products, HFD-590:
Renata Albrecht, M.D., Dep. Div. Dir.
Christina Chi, Ph.D., Project Manager
Daniel Davis, M.D., Medical Officer
Brad Leissa, M.D., Medical Team Leader
Joseph Winfield, M.D., Medical Officer

SUBJECT: The possibility of reopening of Schering's withdrawn NDA 20-574 Vaginal Cream clotrimazole 2% for OTC marketing with the support of Taro's 2% Vaginal Cream. Reconfirmation of the FDA opinion and understanding.

NDA 20-574

DISCUSSION POINTS:

* Reactivation of the withdrawn NDA 20-574 with the following new information and data:
  - one study will be a combination of the 2 Schering clinical studies (previously submitted as part of an original NDA 20-574 which was withdrawn later on) which are currently being pooled and reanalyzed.
  - one ongoing clinical study of Taro will fulfill the second study requirement.
  - one clinical "bridging" study has just been started.

  The FDA agreed to the plan provided that the bridging study can demonstrate comparability between the Taro and Schering formulations.

* FDA's guidance on the appropriateness in using the 2% Schering cream formulation:
  The FDA explained that based on the earlier faxed communication supplied by the sponsor which contained a table comparing the 4 different cream formulations (1% and 2%) of Taro and Schering, it appears that both the creams of Taro and Schering could be considered similar. Therefore there is no objection in using the Schering (2%) cream formulation for marketing. The sponsor will have to send a collated safety information to the FDA on all 1% and 2% cream products, including data from Canada.

* Sponsor stated that they would be marketing the Schering product under NDA 20-574.
  They expressed their gratitude over this brief yet very productive telecon.

/S/

Christina Chi, Ph.D.

12/12/97

cc: Original NDA 20-574
HFD-560/Div.File
HFD-560/TL/HCothran
HFD-560/ClinRev/LChin 12/11/97
HFD-560/PM/SWalther
HFD-590/Div. File
HFD-590/DepDivDir/RAlbrecht
HFD-590/ClinTL/BLeissa 10/6/97 BL 12/12/97
HFD-590/ClinRev/JWinfield
HFD-590/ClinRev/DDavis
HFD-590/PM/Christina Chi

Concurrence only: HFD-590/ClinTL/BLeissa

Drafted and prepared by: CChi 9/29/97 Final: 12/12/97.
TELECON, Schering-Plough Health Care and Taro Pharmaceuticals.

To: Distribution

From: Mary Williams

Date: 10/11/97

Subject: **Minutes of 9/29/97 FDA Teleconference on Clotrimazole 2% Cream NDA**

FDA Participants:

Division of Over The Counter Drug Products:
Ling Chin, M.D.
Helen Cothran
Cheryl Turner, R.N.
Sakineh Walther, R.N.

Division of Special Pathogens and Immunologic Drug Products:
Renata Albrecht, M.D.
Christina Chi, Ph.D
Daniel Davis, M.D.
Brad Leissa, M.D.
Joseph Winfield, M.D.

Sponsor Participants:

Schering-Plough HealthCare Products (SPHCP):
Walter Chambliss, Ph.D.
Joseph Clark, Ph.D.
Ronald Garutti, M.D.
Mary Williams

Taro Pharmaceuticals, Inc.:
Terry Feldman, Ph.D.
Daniel Moros, M.D.
Lorraine Sachs, RAC

Meeting Objective:

- At SPHCP's request, a teleconference was scheduled to discuss and reach agreement on two items in FDA's minutes of the June 18, 1997 meeting regarding SPHCP's and Taro's joint pursuit of a single 2% clotrimazole cream NDA. These two items pertained to the OTC Division's statement that "over 5 years of marketing experience is desired for a product to receive direct OTC marketing approval" and to the FDA's "difficulty extrapolating Taro's safety experience (from their 3-day 2% cream currently marketed in Canada) to support SPHCP's product, because the formulations are different."

Briefing Information:

- Prior to the teleconference, information to support direct OTC marketing of SPHCP's 2% clotrimazole cream formulation for a 3 day treatment of vaginal yeast infections under an approved NDA was submitted to the Agency for their internal review and discussion. This information included safety data for both the active ingredient and the vehicle based on both companies' Rx and OTC marketing history of clotrimazole vaginal products as well as a formula comparison of SPHCP's and Taro's 1 and 2% clotrimazole creams. (Copies of information are attached.)

Discussion and agreements reached:

- During the internal discussions held at FDA prior to the teleconference, the OTC Division and DSPIDP agreed that the information submitted by the sponsors, including the similarity of the four formulas (i.e., SPHCP's and Taro's 1 and 2% clotrimazole creams) and the marketing history of the clotrimazole vaginal products, should be adequate to support the use of SPHCP's 2% clotrimazole cream formulation for direct OTC marketing, provided that the results of the bridge study demonstrate therapeutic equivalency. This decision was conveyed to the sponsors at the start of the teleconference.

- To further support this decision, FDA requested that Taro's safety data for their marketed 2% product in Canada be included in the amendment to SPHCP's withdrawn NDA (#20-574) when it is reactivated.

- The amendment to NDA 20-574, at the time of its reactivation, will also include the reanalysis of the pooled data for the SPHCP clinical studies, the new clinical data for the Taro study, and information on the bridge study currently being conducted. Dr. Winfield concurred with the sponsors' plan to submit only new information. Dr. Chi and Ms. Williams will resolve the administrative details of this submission.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

'ORANDUM Center for Drug Evaluation and Research

Date: 10/7/98

From: Jose Carreras, M.D.
CIB/HFD 344

To: Christina Chi - Project Manager
Joseph Winfield - Medical Officer

Subject: NDA 20-574
Sponsor - Schering Plough
Product - GyneLotrimin 3 Cream 2%

Name of Investigator	Classification
Daniel Wiener, M.D. Montreal, Quebec	VAI
Melvin Guralnick, M.D. Montreal, Quebec	VAI

No objectionable conditions were found which would preclude the use of the data submitted in support of pending NDA.

Note:

VAI = Minor deviation(s) from regulations - Data Acceptable

Jose A Carreras, M.D.

Schering-Plough HealthCare Products

110 Allen Road
Liberty Corner, NJ 07938

Telephone: (908) 604-1952
Fax: (908) 604-1741

CONFIDENTIAL

Please deliver the following 1 pages (including cover page)

DATE:	January 22, 1999
TO:	Ms. Liz Yuan
FAX NUMBER:	301-827-2315
FROM:	Mary Williams
LOCATION:	Liberty Corner, NJ
FAX NUMBER:	908-604-1741

Dear Ms. Yuan:

As discussed earlier today, I am sending a list of concerns/questions regarding a pending CMC supplement to our Gyne-Lotrimin3 Vaginal Cream (NDA 20-574) to be forwarded to your Chemist Reviewer. The issues are of such a nature that I think they would best be handled in a brief teleconference. Please let me know when this can be arranged.

Thank you for your assistance in this matter! /S/

BACKGROUND:

The subject NDA was approved based on the results of two clinical studies: one study was conducted by Schering-Plough HealthCare Products (SPHCP) in the USA, the other study was conducted by Taro in Canada. The formulas used in the two studies were nearly identical with a slight difference in one of the inactive ingredients. However, equivalency was demonstrated in a bridge study which was also provided to the NDA.

OBJECTIVE:

Approval to market Taro's clotrimazole 2% vaginal cream in the USA, which would be produced in Taro's Canadian facility, using their formula, method of manufacture, packaging, and analytical testing. (Note: Taro has produced and marketed their clotrimazole 2% vaginal cream in Canada as an Rx product from 1988 to 1995, and as an OTC product from 1995 to date.

PROPOSAL:

Submit a CMC supplement to the approved NDA, reference the clinical information contained therein, and provide the following Taro information (with any differences from SPHCP highlighted) in support of the above objective: drug substance information; drug product composition page; manufacturing instructions including a typical batch record; in-process and release analytical test methods; packaging information including DMF letters of authorization; and stability report on three marketed batches.

0006

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,

Mary E. Williams /for

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

filed in duplicate
faxed to Ms. Yuan
attachments

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 02/12/99

FROM: Charlotte Yaciw, Chemist, HFD-830/550
Dorota Matecka, Chemist, HFD-830/590

THROUGH: Hasmukh Patel, Team Leader, HFD-550 HBP 2/12/99

TO: Mary Williams, Schering Health Care Products

SUBJECT: Proposal presented in FAX dated January 22, 1999 concerning NDA 20-574, 2% clotrimazole vaginal cream

We are evaluating your proposal, however, we feel that we need additional information in order to fully understand the scope of the intended change. Please provide comparison tables for the Schering and Taro formulations for the following:

Current formulation
Method of manufacture for the product
Specifications and methodology
Container/closure system
Labeling

Please FAX this information to Ms. Elizabeth Yuan at 301-827-2315 as soon as possible. We will contact you when we have evaluated this information.

APPEARS THIS WAY
ON ORIGINAL

HFD 590 GII

MEMORANDUM OF TELECONFERENCE

Meeting Date:	3/19/1999
Time:	2:30pm
Location:	Room S 300 APR 15 1999 9201 Corporate Blvd. Rockville, MD 20851
Application:	NDA 20-574, Gyne-Lotrimin 3 Vaginal Cream
Type of Meeting:	Guidance to industry
Meeting Chair:	Maria R. Cook, M.B.A
Meeting Recorder:	Elizabeth F. Yuan, R.Ph.

FDA Attendees, titles, and Office/Division:
Renata Albrecht, M.D., Deputy Division Director, HFD-590
Christina H. Chi, Ph.D., Project Manager, HFD-590
Ling Chin, M.D., M.P.H., Medical Officer, HFD-560
Maria R. Cook, M.B.A., Supervisory Project Manager, HFD-560
Ellen Frank, R.Ph., Supervisory Project Manager, HFD-590
Beverly Friedman, Senior Program Management Officer, HFD-5
Don Hare, Special Assistant to the Director, Office of Generic Drugs, HFD-604
Mike Jones, Senior Program Management Officer, HFD-5
Linda M. Katz, M.D., M.P.H., Deputy Division Director, HFD-560
Brad G. Leissa, M.D., Medical Team Leader, HFD-590
Dorota M. Matecka, Ph.D., Chemistry Reviewer, HFD-590
Hasmukh Patel, Chemistry Team Leader, HFD-550
Charlotte Yaciw, Chemist, HFD-550
Elizabeth F. Yuan, R.Ph., Assistant Regulatory Mgmt. Officer, HFD-560

External Constituent Attendees and titles:
Mary Williams, Associate Director, Regulatory Affairs, SPHCP
Dr. Joseph Clark, Consultant, SPHCP

Dr. Terry Feldman, Vice President, Research and Development, Taro Pharmaceuticals
Derrick Ganes, Vice President, Regulatory Affairs, Canada
Dr. Daniel Moros, Vice Chairman, Taro Pharmaceuticals
Ms. Lorraine Sachs, Senior Regulatory Affairs Scientist, Taro Pharmaceuticals
Avraham Yacobi, Chairman and President, Taro Research Institute

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 teatment 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 bridging study comparing the different SPHCP and Taro formulations was conducted. The results of the study demonstrated the equivalency of the two formulations."

(from SPHCP's 2/19/1999 fax to the Agency)

Meeting Objective:
To address Schering Plough's request for guidance to approve an additional formulation manufactured by Taro, under NDA 20-574, Gyne-Lotrimin 3 Vaginal Cream.

Discussion Points

1. Taro's clotrimazole formulation cannot be submitted persuant to 505 (b) (2) of the Food, Drug, and Cosmetic Act because FDA's regulations prohibit the submission of a 505 (b) (2) application for a duplicate of a listed drug that is eligible for approval as an ANDA. (See 21 CFR 314.101 (b) (9)). Further, a 505 (b) (2) application would not be appropriate because Taro would have a right of reference to the data required for approval.

2. A 505(b) (1) NDA application can be submitted with half User Fee if Schering grants Taro a right of reference to Schering's safety and efficacy data in Schering's NDA 20-574 (Taro should have a right of reference to their own data in Schering's application). The application would be assigned a new NDA number. It will be considered a standard application with a full CMC submission. The clinical section data will be in reference to NDA 20-574. This application will have a 12 month goal date, however, the Agency will target to complete within 10 months.

3. A 505(j) ANDA submission can be submitted to the Agency. However, sponsor understands that if the sponsor decides to pursue this route, then they would have to submit a controlled correspondence to Doug Sporn, Office of Generic Drugs, to determine if the bioequivalence study that was used to support the NDA approval will be accepted as the bioequivalence study used to support ANDA approval.

4. With regards to exclusivity, Schering can waive their exclusivity specifically to Taro. Taro's formulation, if approved under 505 (b) (1) of the Food, Drug, and Cosmetic Act, then they will be granted the remainder

of Schering's exclusivity until November 24, 2001 ("umbrella policy"). For clarification, see page 28897 of FR Vol. 54 No. 130, July 10, 1989.

5. Taro's drug product would be rated as AB to the Schering Gyne-Lotrimin 3 Vaginal Cream if approved as either an ANDA or NDA.

Decisions (agreements) reached:
Sponsor will notify the Agency of which approach they wish to pursue the approval of the Taro formulation of the Clotrimazole 2% cream.

Minutes Preparer: ey3/23, 4/7, 4/15/1999

/S/ 4/19/99
Chair Concurrence:

APPEARS THIS WAY
ON ORIGINAL

To: Distribution

From: Mary Williams

Date: 3/24/99

Subject: **Minutes of 3/19/99 Teleconference with FDA To Discuss Concurrent Marketing of a Taro and a SPHCP Clotrimazole Vaginal Cream, 2%, Product in the USA**

FDA Participants:

Renata Albrecht	Deputy Division Director/ DSPIDP
Christina Chi	Project Manager/ DSPIDP
Ling Chin	Medical Officer/ DOTCDP
Rosemary Cook	Supervisory Project Manager/ DOTCDP
Ellen Frank	Supervisory Project Manager/ DSPIDP
Beverly Friedman	Senior Program Management Officer/ User Fee Staff
Don Hare	Consumer Safety Officer/ Office of Generic Drugs
Mike Jones	Senior Program Management Officer/ User Fee Staff
Linda Katz	Deputy Division Director/ DOTCDP
Brad Leissa	Medical Team Leader/ DSPIDP
Dorota Matecka	Chemist/ ONDC
Hasmukh Patel	Chemistry Team Leader/ ONDC
Charlotte Yaciw	Chemist/ ONDC
Elizabeth Yuan	Project Manager/ DOTCDP

Sponsor Participants:

Schering-Plough HealthCare Products (SPHCP):

Joseph Clark	Consultant
Mary Williams	Associate Director Regulatory Affairs

Taro Pharmaceuticals, Inc.:

Terry Feldman	V.P. Research & Development, Canada
Derrick Ganes?	V.P. Regulatory Affairs, Canada
Daniel Moros	Vice Chairman
Lorraine Sachs	Senior Regulatory Affairs Scientist
Avraham Yacobi	Chairman & President Taro Research Institute

Meeting Objective:

In a February 19, 1999, General Correspondence submission (copy of cover letter attached), SPHCP requested FDA guidance on the requirements for approval to concurrently market two similar clotrimazole vaginal cream, 2%, products in the USA. One of the products is currently manufactured and marketed by Taro Pharmaceuticals, Inc. in Canada. The other product is currently manufactured and marketed by SPHCP in the USA under a recently approved NDA, which was granted 3 years of marketing exclusivity. Following an internal meeting, FDA arranged a teleconference with the sponsors to discuss the various options.

Background:

SPHCP and Taro co-sponsored the clinical studies provided in the recently approved Gyne-Lotrimin® 3 Vaginal Cream, NDA #20-574. 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 by Taro in Canada since 1989. Because the Taro formula differed slightly from the SPHCP formula, FDA requested that a bridge study be conducted to compare the two formulations. The results, which FDA agreed demonstrated the equivalency of the two formulations, were provided to the NDA.

As part of the original joint business agreement between SPHCP and Taro, SPHCP is required to manufacture the subject product for Taro distribution in the USA. However, both companies have since determined that for business reasons, it is more advantageous for each company to manufacture and market their own product in the USA, i.e., for Taro to manufacture and market their existing Canadian product in the USA, and for SPHCP to continue manufacturing and marketing the product as currently approved in the NDA.

Discussion:

The FDA opened the discussion by thanking the sponsors for the information provided in the 2/19/99 general correspondence. Subsequently, representatives from the relevant FDA Divisions met to discuss the various options and determined the following:

1. The sponsor's suggestion of filing a 505(b)(2) submission is not possible according to 21 CFR 314.101(d)(9) which states that the FDA may refuse to file an application that "is submitted as 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act."

2. It is possible to file an original NDA under 505(b)(1) which would contain Taro's CMC information and reference the clinical data contained in NDA #20-574. This submission would be subject to one-half of the full User Fee and would have a 12 month review clock. When asked why it would take 12 months to review, considering the clinical review was already completed, the FDA responded that the submission would still be considered a new NDA, and therefore subject to a 1 year review clock. However, they indicated that their 1999 internal goal for reviewing an NDA is 10 months, and that it was possible to achieve or even exceed this 10 month goal, but they made no committment.

   When asked how an original Taro NDA would affect SPHCP's marketing exclusivity, FDA stated that a definitive answer had not been reached on this question, but their current thinking was that Taro's NDA would fall under a SPHCP umbrella. This would result in the expiration of the marketing exclusivity period for both companies at the end of the 3 year exclusivity period granted to SPHCP's NDA, i.e. November 24, 2001.

3. It is possible to file an ANDA but it would require that SPHCP waive their exclusivity rights. In addition, Taro would have to submit a "controlled correspondence" to the Generic Division with their proposal on how bioequivalency would be demonstrated. The FDA indicated that the use of Taro's clinical study would not be permitted to support bioequivalence in the ANDA since had been previously used to support the original

NDA. However, the bridge study which Taro had also conducted may be allowed to demonstrate bioequivalence.

The sponsors thanked the Agency participants for their guidance which will be helpful in determining an appropriate course of action.

c. Foreign Marketing History

Taro Pharmaceuticals Inc. markets Clotrimazole Vaginal Cream in 1% and 2% formulations in Canada and in a 1% formulation in the United States. The Canadian products had been marketed as prescription products from 1988 to 1995, at which time they were granted over-the-counter status by the Canadian Health Protection Branch (HPB). The U.S. 1% product has been marketed as an over-the-counter product since 1995 under ANDA 72-641.

A 10% Clotrimazole Vaginal Cream (Canesten) has been marketed in Canada by Bayer Inc. since February 1995.

A 10% Clotrimazole Vaginal Cream (Canesten) is also marketed by BayPharm, UK (Martindale, Extra Pharmacopeia, 29th edition, 1989, page 421-422).

Taro confirms that the drug Clotrimazole Vaginal Cream USP, 2% has never been withdrawn from market for safety or [redacted] reasons.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: July 6, 1999

To: Taro Pharmaceuticals Inc.
Att: Kalpana Rao

From: Dorota Matecka, Ph.D., Chemistry Reviewer
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: NDA 21-143 (clotrimazole vaginal cream, 2%)

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):

[redacted]

Drug product (clotrimazole vaginal cream):

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

Please specify the function of:

[redacted]

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: December 2, 1999

To: Taro Pharmaceuticals Inc.
Att: Kalpana Rao

From: Dorota Matecka, Ph.D., Chemistry Reviewer
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Through: Norman R. Schmuff, Ph.D., Chemistry Team Leader
Division of Special Pathogens and Immunologic Drug Products, HFD-590 NRS 12/7/99

Re: NDA 21-143 (clotrimazole vaginal cream, 2%)

Please address the following CMC comments regarding the drug product (clotrimazole vaginal cream, 2%):

1. Please provide the results, detailed description (protocol) and the method validation package for the method used to conduct Microbiological Examination of the drug product, clotrimazole vaginal cream, 2%.

2. Please provide the results and the protocol of the Antimicrobial Preservative Effectiveness Testing conducted on the drug product, clotrimazole vaginal cream, 2%.

3. Please provide batch analysis data for all the manufactured batches of the drug product, clotrimazole vaginal cream, 2%.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-143

JAN 21 2000

MEMORANDUM OF TELECON

DATE: December 13, 1999

APPLICATION NUMBER: NDA 21-143, Clotrimazole Cream, 3 day vaginal cream, 2%.

BETWEEN SPONSOR:

Taro Pharmaceuticals USA, Inc.:
Lorraine W. Sachs, Associate Director, Regulatory Affairs

AND FDA:

Division of Over the Counter Drug Products, HFD-560:
Helen Cothran, Team Leader
Daniel Keravich, M.S., M.B.A., Project Manager
Kerry Rothschild, J.D., Project Manager
Cheryl A. Turner, R.N., Interdisciplinary Scientist

Division of Special Pathogen and Immunologic Drug Products, HFD-590:
Christina Chi, Ph.D., Project Manager
Brad G. Leissa, M.D., Medical Team Leader
Joseph K. Winfield, M.D., Medical Officer

SUBJECT: FDA's request to Taro Pharm. for additional information for their pending NDA 21-143.

DISCUSSION POINTS:

- The Agency requested the safety data of clotrimazole vaginal cream, 2%, from two sources:
  (1) the post-marketing reports of Gyne-Lotrimin-3 (Schering product) since it was approved on November 25, 1998, up to now,
  (2) the post-marketing reports of Clotriderm, vaginal clotrimazole cream, 2%, marketed by the Canadian subdivision of Taro.
  The Agency explained that Taro's submision of August 25, 1999, which mentioned that there were no other safety update information beyond what was submitted for the Gyne-Lotrimin-3 application, the clinical studies conducted by both Taro and Schering, was not the information the Agency anticipated. The sponsor replied that they will try to get the requested data.

- The Agency advised the sponsor to look for at least 2 (two) additional prospective names for the product and send them to the Agency as soon as possible. The sponsor responded that they have been working on it, and will send them to the Agency soon.

- The Agency explained that at present not all the disciplines have completed their review of this application, therefore, any labeling discussion will not necessarily mean that it will receive an approval action. Since the OTC's ruling on the Drug Facts Format is in effect as of October 17, 1999, the Agency urged the sponsor to present the carton labeling of this product according to GyneLotrimin-3 labeling content but in the Drug Facts Format. The sponsor answered that it will be done and submitted in mid January 2000.

The telecon was adjourned amicably.

/S/ 1/31/2000

Christina Chi, Ph.D.

Concurrence by: /S/ HFD-590/TL/BLeissa.

Attachment: Fax to Taro Pharm. re: FDA telecon attendees.

cc: Original NDA 21-143

HFD-560/Div.File
HFD-560/TL/HCothran
HFD-560/PM/DKeravich
HFD-560/PM/KRothschild
HFD-560/IS/CTurner12/15/'99

HFD-590/Div.File
HFD-590/ClinTL/BLeissa
HFD-590/ClinRev/JWinfield
HFD-590/PM/Christina Chi

Drafted and prepared by: CChi 12/14/99

TELECON, Taro Pharmaceuticals, USA.

Note: This meeting minutes was sent out as [ ]attachment to participant on 12/14/1999. From 12/16/99 till 1/30/2000 there was no reply received, therefore, this meeting minutes is now considered official.

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 2/1/00

NDA#: 21-143

Name of Drug: Trivagizole-3®
(clotrimazole vaginal cream, 2%)

NDA Holder: Taro Pharmaceuticals U.S.A., Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590) on November 19, 1999, to review the proposed proprietary drug name, Trivagizole-3® in regard to potential name confusion with existing proprietary/generic drug names.

The firm has submitted a total of nine proposed proprietary names. The chronology of proposed names: 1. Original proposal: Clotriderm (product's trade name in Canada), 2) Clotrimazole Vaginal Cream USP, 2%, 3) Tarozole (sounds very similar to Terazole®, an Rx vaginal product by Ortho), 4) Gyne Lotrimin III (sounds very similar to Gyne Lotrimin 3), 5) Fem Clotrimin III (sounds very similar to Fem Care by Schring containing 1% clotrimazole). The firm was advised that all the above proposed proprietary names except (2) are not acceptable. The firm comes back with another five proposed names: 1) Vagizole-3, 2) Trivagizole-3, 3) Trifemizole-3, 4) Clofmin-3, 5) Clotrimistat-3. The firm would prefer to have either Vagizole-3 or Trivagizole-3 approved as the chosen proprietary name.

The Labeling and Nomenclature Committee (LNC) had NOT reviewed this proprietary name. This consult was forwarded to OPDRA for final clearance prior to approval of NDA. The goal date is 4/17/00.

PRODUCT INFORMATION

Trivagizole-3 comes as a clotrimazole vaginal cream , 2% with one reusable applicator. The intended dose is for a 3 day treatment for most vaginal yeast infection.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, ® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (updated monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online, Decision Support System (DSS), Establishment Evaluation System, and LNC database . An OPDRA expert group was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process. Inpatient orders study were not done since Trivagizole is an OTC product which is used mostly on an outpatient basis.

A. EXPERT PANEL DISCUSSION:

The group did raise concern on the proposed name, Vigizole, which sounds very similar to Vagisil®. It is a topical local anesthetic currently marketed by Combe. The group objected to the use of proposed name Vagizole and recommended doing prescription study on Trivagizole only since Vagizole and Vagisil sound very similar and look-alike in written orders. This poses a significant risk of mix-up between these two names, which may contribute to medication errors.

B. STUDY CONDUCTED BY OPDRA

Methodology:

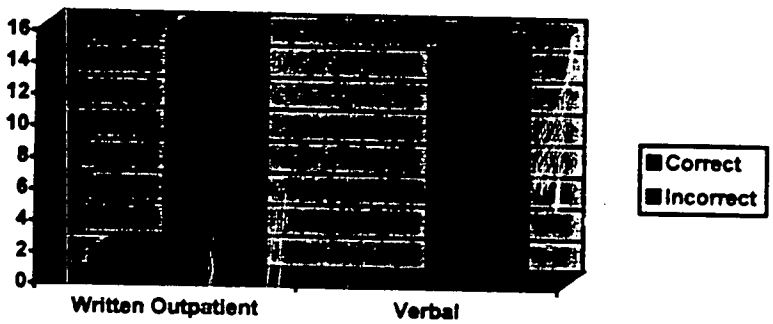
This study involved 46 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Trivagizole® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An OPDRA staff member wrote two outpatient prescriptions, each consists of a known drug product and a prescription for Trivagizole®. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions were sent to 23 participants for review. In addition, one pharmacist with a foreign accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to 23 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the

medication error staff. We recognized that our sampling is small and the study is trying to set up for failure.

The results are summarized in Table I.

Table I

Study	# of Samples	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	23	18 (78%)	2	16
Verbal	23	15 (65%)	0	15
Total	46	33 (72%)	2	31



Six percent of the participants responded with the correct name Trivagizole-3®. The incorrect written and verbal responses are as follows in Table II :

Table II

	Incorrectly Interpreted
Written	Furzigole-3
	Furazycle-3
	Furazigel-3
	Luragizole-3
	Triragizole-3 (2)
	Triragyale-3
	Trivagyride-3
	Trivagycle-3
	Turagzale-3
	Turazgizole-3

	Trinagizole-3
	Turagizole-3 (4)
Verbal	Trivagsil-3
	Triphasil
	Trivagisil-3 (10)
	Trivagel (2)
	Tirragacil-3

C. CONTAINER LABEL, CARTON AND INSERT LABELING:

The established name, clotrimazole vaginal cream (2%), container label is supposed to be half as big as the proprietary name, Trivagizole. But it measures only ¼ as big as the proprietary name. Carton and insert labeling also measure only ¼ of the proprietary name.

D. CONCLUSIONS:

The results of the verbal and written analysis studies show two participants interpreted the proprietary name Trivagizole-3® correctly. There were sixteen and fifteen incorrect interpretations for written and verbal orders. However, there was no overlap existing approved products uncovered in our study. Even though there were thirty-one incorrect or misspelled interpretations, these responses pose little concern since these products are not currently marketed. Finally, the studies and searches conducted within FDA did not reveal any existing drug names that would render the proposed proprietary name, Trivagizol-3® objectionable. In general, we do not recommend the use of suffix number in a proprietary name. However, in many existing topical vaginal products, suffix is used to indicate the length of therapy such as the following products that are currently marketed; Monistat-3, Vagistat-1, Terazol-3 and Femstat 3.

III. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name Trivagizole-3®.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 2/7/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 11/19/99	DUE DATE: 2/7/00	OPDRA CONSULT #: 99-093

TO (Division):
Mark Goldberger, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

Through: Christina Chi, Project Manager
HFD-590

PRODUCT NAME: Trivagizole-3® (clotrimazole vaginal cream, 2%) NDA #: 21-143	MANUFACTURER: Taro Pharmaceuticals U.S.A., INC.
Safety Evaluator: Peter Tam	

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of proprietary name Trivagizole-3®.

/S/ 2/7/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 2/8/00

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

MEMORANDUM
March 15, 2000

NDA: 21-143
DRUG: **Clotrimazole vaginal cream**

The NDA review is acceptable in an abbreviated form. This is an old product and the Sponsor had right of reference to previous pharmacology/toxicology data. No additional nonclinical pharmacology/toxicology data was submitted.

/S/

Kenneth L. Hastings, D.V.P.H.
Pharmacology/Toxicology Team Leader
DSPIDP/ODE IV

APPEARS THIS WAY
ON ORIGINAL

APR 12 2000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: April 12, 2000

From: Brad Leissa, MD
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: Taro Pharmaceuticals' **Trivagizole 3™** (2% clotrimazole vaginal cream, **NDA 21-143**) approval for over-the-counter use.

At the time (November 1998) Schering received OTC marketing authorization for Gyne-Lotrimin 3 (2% clotrimazole vaginal cream, NDA 20-574), this approval was based on clinical data supplied by both Schering and Taro Pharmaceuticals. In addition, a smaller bioequivalence study (using clinical endpoints) established similar clinical safety and efficacy for Schering's and Taro's formulations of clotrimazole vaginal cream. This small study was referred to as a "bridging" study and confirmed that data from the larger clinical trials supplied by Schering and Taro could be used. Subsequently, Schering granted Taro right of reference to these data.

At the time NDA 21-143 was submitted, Taro's 2% clotrimazole vaginal cream already had extensive post-marketing experience in Canada. Taro's safety update amendment reassured the Agency that no serious safety problems are apparent with Taro's 2% clotrimazole vaginal cream. Hence, based on clinical trial from Taro and Schering (by right of reference) and "foreign" post-marketing experience, Taro has demonstrated substantial evidence for safety and efficacy for their product.

On April 3, 2000 Taro Pharmaceuticals requested a full waiver for the requirement to provide data in support of a pediatric labeling as per 21 CFR § 315.55 (c). In their letter, Taro argued that "*The drug product...does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients...*"

However, the Division agrees to waive the pediatric labeling requirement for girls <12 yo using a different rationale: Taro's Trivagizole 3™ approval is for OTC use only. In the OTC setting, treatment decisions are frequently made without the guidance of a healthcare provider. If a prepubescent girl develops a vulvovaginal yeast infection, it is very important that the diagnosis and treatment of this condition takes place under the guidance of a healthcare provider. As alluded to above, other very important medical and psychosocial events are likely associated with the condition.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 27, 2000

FROM: Christina H. Chi, Ph.D.

SUBJECT: DSI's audit of pivotal clinical studies of NDA 21-143, Trivagizole 3™ Vaginal Cream, Clotrimazole Vaginal Cream 2%

TO: The File of NDA 21-143, Trivagizole 3™ Vaginal Cream, Clotrimazole Vaginal Cream 2%

All clinical studies which support NDA 21-143, Trivagizole 3™ Vaginal Cream, Clotrimazole Vaginal Cream 2% are the exact same studies which were used to support NDA 20-574, Gynelotrimin 3™ Vaginal Cream, Clotrimazole Vaginal Cream 2%.

These clinical studies of NDA 20-574 had been audited and was found satisfactory (memorandum from Jose Carreras, M.D., CIB/FFD-344 dated October 7, 1998).

APPEARS THIS WAY
ON ORIGINAL