CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-143

MEDICAL REVIEW

DATE SUBMITTED BY SPONSOR: JUNE 16, 1999
DATE RECEIVED BY CDER: JUNE 17, 1999
DATE RECEIVED BY REVIEWER JULY 19, 1999
DATE REVIEW STARTED: OCTOBER 4, 1999
DATE REVIEW COMPLETED: DECEMBER 16, 1999
DATE REVISED REVIEW COMPLETED: MARCH 13, 2000

MEDICAL OFFICER'S REVIEW OF NDA 21-143

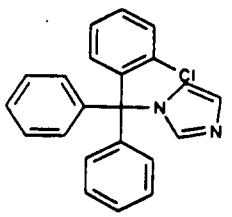
APPLICANT: Taro Pharmaceuticals Inc.
130 East Drive
Bramalea, Ontario, L6T1C3
Canada

GENERIC NAME: Clotrimazole Vaginal Cream 2%

TRADE NAME: Trivagizole 3

CHEMICAL NAME: 1 (0-chloro-alpha,alpha-diphenyl benzyl) imidazole

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{22}H_{17}ClN_2$

MOLECULAR WEIGHT: 344.84

PHARMACOLOGIC CATEGORY: Antifungal

DOSAGE FORM: Vaginal Cream

ROUTE OF ADMINISTRATION: Vaginal

PROPOSED INDICATION AND USAGE: Trivagizole 3 is an OTC drug indicated for a 3-day treatment of vaginal candidiasis.

PROPOSED DOSAGE : One applicatorful (100 mg) for three 3 consecutive nights.

RELATED DRUGS: INDs [redacted]
NDAs 17-613; 17-619; 17-717; 18-052; 18-813; 18-827; [redacted] 20-010; 20-525; 20-526

MATERIAL REVIEWED: 1 Volume

BACKGROUND

This NDA is submitted by Taro Pharmaceuticals, Inc. seeking approval to market Clotrimazole Vaginal Cream USP, 2%, which is an approved over-the-counter (OTC) product marketed as Gyne-Lotrimin 3® and is indicated for a 3-day treatment of vaginal candidiasis.

The safety and efficacy data (including preclinical, toxicology and clinical data) for this NDA is contained in the approved Schering-Plough Health Care (SPHCP) NDA 20-574 for Gyne-Lotrimin 3®. Therefore, only the Chemistry, Manufacturing and Controls (CMC) and labeling for Trivagizole 3 was submitted by Taro to this NDA.

NDA 20-574 was approved based upon two pivotal clinical studies that were co-sponsored by SPHCP and Taro. SPHCP's studies (93-34 and 93-40) were combined and analyzed according to guidelines established by SPHCP and the review division (DSPIDP) of FDA and was considered as a single pivotal study for NDA 20-574. Taro's study (95-50) was analyzed using the same evaluability criteria that was applied to the SPHCP's pooled study and considered as the second pivotal study. The pivotal studies compared the clinical, mycological and therapeutic cure rates of clotrimazole 2% cream when used for 3-day and clotrimazole 1% cream when used for 7-days.

Since the formulation of SPHCP's clotrimazole 2% cream differed slightly from Taro's clotrimazole 2% cream, the sponsors conducted a bridging study (CTZ 97-01) in order to demonstrate therapeutic equivalence between their respective formulation of the 2% ciotrimazole vaginal cream when used for 3-days. The results of this study demonstrated that the two products were therapeutically equivalent. Based on the results of the two pivotal studies and the bridging study, Gyne-Lotrimin 3® (Clotrimazole Vaginal Cream USP, 2%) was approved as an OTC product on November 25, 1998.

A summary of the efficacy and safety results of NDA 20-574 is provided in this review for immediate reference only, a complete review of the efficacy and safety data is found in the Medical Officer's Review of NDA 20-574 dated September 21, 1998.

EFFICACY

The efficacy database for NDA 20-574 included data analyses based on the revised criteria of patients who satisfied all of the following criteria in each of the clinical studies.

1. Received exposure to the study drug for either 3 or 7 days depending on the treatment group.

2. Returned for at least one follow-up evaluation, i.e., returned for visit 2 and /or visit 3. Visit 2 was defined as any visit 10-17 days after the start of therapy and visit 3 was defined as any visit 25-35 days after the start of therapy.

3. Had a pre-therapy 10% KOH wet mount positive for *Candida* pseudohyphae and pre-therapy vaginal culture positive for *Candida.* (If the wet mount and culture were not in agreement, the culture results were used.)

4. Had not used either a systemic or topical (intravaginal) antifungal drug, except for her assigned therapy, between the time of starting therapy and completing her participation in the study. If a systemic or topical antifungal drugs were used, the visit(s) occurring after first use of the drugs was(were) considered not assessable for the efficacy analyses.

The Agency and Sponsor agreed that the primary efficacy endpoint would be the therapeutic cure rate. Clinical and mycological cures would be secondary endpoints. Definitions of mycological, clinical and therapeutic cure may be found in the Clinical Studies section of the Medical Officer's Review of NDA 20-574.

Given in Table 1 are the clinical, mycological and therapeutic cure rates obtained in the combined studies 93-34 and 93-40 and in study 95-50. The table also gives the 95% confidence limits on the difference between the 7-day 1% and the 3-day 2% therapies. The results indicate that the 3-day 2% clotrimazole is at least equivalent to the 7-day 1% therapy and that the 95% confidence limits fall within the ± 20% range.

Table 1

Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

COMBINED 93-34 & 93-40	**CLOTRIMAZOLE 2% 3-DAY**	**CLOTRIMAZOLE 1% 7-DAY**	**1% 7-DAY VS 2% 3-DAY 95% CI**
Clinical Cure	188/219(86%)	193/217 (89%)	-10, 4
Mycological Cure	109/219(50%)	115/217(53%)	- 13, 7
Therapeutic Cure	**103/219(47%)**	**109/217(50%)**	**-13, 7**
Study 95-50			
Clinical Cure	67/74(91%)	71/77(92%)	-11, 9
Mycological Cure	49/69(71%)	49/74(66%)	-12, 21
Therapeutic Cure	**48/74(65%)**	**47/77 (61%)**	**-13, 20**

The results of the bridging study comparing the therapeutic effectiveness of the two formulations of 2% clotrimazole vaginal cream (Taro and Schering) used once daily for three days demonstrate that the products are equally effective treatments of vulvovaginal candidiasis (Table 2). There were no significant differences between the two formulations with regard to in clinical, mycological or therapeutic cure rates.

Table 2
Study CTZ 97-01
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	CLOTRIMAZOLE TARO 2% 3-DAY	CLOTRIMAZOLE SCHERING 2% 3-DAY	TARO 2% 3-DAY VS SCHERING 2% 3-DAY 95% CI
Clinical Cure	51/66(77%)	53/68(78%)	-15, 14
Mycological Cure	51/66(77%)	51/68(75%)	-12, 17
Therapeutic Cure	**43/66(65%)**	**42/68 (62%)**	**-13, 20**

SAFETY

This safety summary includes all data as provided by the sponsor from clinical investigations conducted in the United States and Canada to evaluate intravaginal 3-day therapy with clotrimazole cream.

The clinical program to evaluate the safety and efficacy of self-administered clotrimazole cream once-a-day for three consecutive days for the treatment of vulvovaginal candidiasis consisted of three well-controlled studies conducted by Schering-Plough HealthCare Products (SPHCP). The first and second studies (protocol 92-11 and 93-34) compared 1% (50 mg/day), 2% (100 mg/day), and 4% (200 mg/day) clotrimazole cream for 3 days to 1% (50 mg/day) clotrimazole cream for 7 days. The third study (protocol 93-40) compared the 7-day 1% therapy and the 3-day 1% and 2% therapies.

Through a business arrangement, SPHCP acquired the rights to use the data from a clinical trial conducted by Taro Pharmaceuticals U.S.A., Inc. (Taro). This fourth well-controlled study (protocol 95-50) conducted by Taro compared a 3-day 2% therapy (nearly identical to the 3-day 2% cream used in the SPHCP studies) with the same 7-day 1% therapy used in the SPHCP studies. The 7-day 1% product was the FDA approved (NDA 18-052) over-the-counter SPHCP clotrimazole cream product (Gyne-Lotrimin® Vaginal Cream) for treatment of self-diagnosed vaginal candidiasis for non-pregnant women.

A fifth (bridging) study was conducted by Taro Pharmaceutical U. S. A., Inc. at the request of the FDA to demonstrate clinical equivalence between the two 2% formulations. This study compared the 3-day 2% clotrimazole cream manufactured by Taro to the 3-day 2% cream manufactured by Schering.

The safety database included 1063 patients enrolled in studies 92-11, 93-34 and 93-40 (324, 7-day 1%; 323, 3-day 1%; 314, 3-day 2%; 102, 3-day 4% therapy) All patients used at least one dose of their assigned therapy. The Taro clotrimazole safety database included 353 patients enrolled in study 95-50 (87, 7-day 1%; 90, 3-day 2%; 87, 1-day 2% therapy and 89, 1-day 500 mg vaginal tablet).

In the bridging study (CTZ 97-01) conducted by Taro, the safety database included 147 patients. Seventy-four received Taro's 3-day 2% clotrimazole cream and 73 received Schering's 3-day 2% cream.

Total patients (combining all studies) included in the safety database by treatment are as follows:

Patients	Treatment Group
411	7-day, 1% cream
551	3-day, 2% cream
323	3-day, 1% cream
102	3-day, 4% cream
87	1-day, 2% cream
89	1-day. 500 mg vaginal tablet

In all studies, adverse events reported by the patients or observed by the investigators were characterized by their severity and the investigators' assessments of their relationship to the use of study drug. Treatment-related adverse events were those which were classified as either possibly, probably or definitely related to treatment. In study 92-11, adverse events and concomitant illnesses were recorded separately, whereas in studies 93-34 and 93-40 they were recorded under "Adverse Events". In study 92-11, assessments of the causal relationship of concomitant illnesses to treatment were neither provided by the investigators nor made by the Sponsor. In Taro studies 95-50 and 97-01 all adverse events/concomitant illnesses reported by the patients or observed by the investigators were assessed as to the use of the study drug.

Discontinuations From Treatment

Of the 1063 patients in SPHCP studies (324, 7-day 1%; 323, 3-day 1%; 314, 3-day 2%; 102, 3-day 4% therapy) who used at least one application of clotrimazole cream. 2 (0.2%) did not complete their course of therapy:

1. Patient No. 66 (study 92-11, 3-day 1% therapy) reported she stopped therapy after two doses because of vaginal irritation and spotting.

2. Patient No 459 (study 93-34; 7-day 1% therapy) did not take her first dose of study drug until 9 days after it was dispensed to her. The patient reported

spotting after her first dose of clotrimazole and discontinued further use of the drug.

In the Taro 95-50 study only one patient (No. 222; 1-day, 500 mg vaginal tablets) discontinued participation due to a treatment-related adverse event (vulvo-vaginal pruritis and burning) which got worse after treatment. This occurred one day after treatment with the vaginal tablet and was considered definitely related to the study drug.

In Taro study 97-01 no patient discontinued the study drug due to and adverse event.

Adverse Events/Concomitant Illnesses

Two adverse events that met the definition of a serious adverse event were reported. Both events involved hospitalizations for reasons that were judged by the investigators to be unrelated to treatment:

1. Patient No. 281 (study 93-40; 7-day 1% therapy) was hospitalized for a bilateral thoracic sympathectomy 21 days after the start of therapy.

2. Patient No. 477 (study 93-40; 3-day 1% therapy) was hospitalized for abdominal pain 6 days after the start of therapy, at which time it was determined that she was pregnant. Urine and serum pregnancy tests performed before the start of therapy were negative. No information on the outcome of her pregnancy was provided by the investigator. The patient was dropped from the study.

In addition to the three patients listed above who discontinued treatment because of adverse events, 7 patients (2, 7-day 1% therapy; 2, 3-day 1%; 3, 3-day 2% therapy), who completed their course of therapy, were discontinued at their first follow-up evaluation because of adverse events:

1. Patient No. 42 (study 93-34; 7-day 1% therapy) reported burning of the vulva and dysuria of 3 days duration starting on the first day of therapy

2. Patient No. 50 (study 93-34; 7-day 1% therapy) had otitis media with onset on the fifth day of therapy.

3. Patient No. 499 (study 93-34, 3-day 2% therapy) developed a vaginal discharge with a fishy odor 14 days after the start of therapy.

4. Patient No. 584 (study 93-34; 3-day 1% therapy) had bronchitis with onset on the fifth day of therapy.

5. Patient No. 138 (study 93-40; 3-day 2% therapy) reported vaginal swelling, itching and redness 3 days after the start of therapy

6. Patient No 379 (study 93-40; 3-day 2% therapy) developed a urinary tract infection 10 days after the start of therapy.

7. Patient No 477 (study 93-40: 3-day 1% therapy) was hospitalized 6 days after the start of therapy (see above).

For each study Table 3 gives the overall incidence of adverse events, regardless of causality.

Table 3
Overall Incidence of Adverse Events - All Studies

STUDY	7-Day 1%		3-Day 1%		3-Day 2%		3-Day 4%		1-Day 2%		1-Day 500 mg Vaginal Tablet		1-Day Diflucan 150 mg	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
92-11	56	11	52	15	52	21	54	7	-	-	-	-	-	-
93-34	137	34	138	39	131	30	48	42	-	-	-	-	-	-
93-40	131	11	133	13	131	14	-	-	-	-	-	-	-	-
95-50	87	3	-	-	90	2	-	-	87	2	89	7	88	2
97-01(TARO)	-	-	-	-	74	1	-	-	-	-	-	-	-	-
97-01 (SCH)	-	-	-	-	73	-	-	-	-	-	-	-	-	-

N = number of patients

The overall incidence of adverse events was similar across treatment groups.

Table 4 gives the overall incidence of adverse events that were judged by the investigators to be treatment-related.

Table 4
Overall Incidence of Treatment-Related Adverse Events - All Studies

STUDY	7-Day 1%		3-Day 1%		3-Day 2%		3-Day 4%		1-Day 2%		1-Day 500 mg Vaginal Tablet		1-Day Diflucan 150 mg	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
92-11	56	5	52	8	52	8	54	2	-	-	-	-	-	-
93-34	137	9	138	9	131	8	48	13	-	-	-	-	-	-
93-40	131	2	133	0	131	1	-	-	-	-	-	-	-	-
95-50	87	0	-	-	90	0	-	-	87	1	89	3	88	2
97-01(TARO)	-	-	-	-	74	1	-	-	-	-	-	-	-	-
97-01 (SCH)	-	-	-	-	73	-	-	-	-	-	-	-	-	-

N = number of patients

The incidence of treatment-related adverse events for each treatment group were similar. The most frequently occurring treatment-related adverse events were itching, burning and irritation. Treatment-related adverse events which were judged to be severe were reported for 9 patients (2, 7-day 1% therapy; 4, 3-day 1% therapy; 2, 3-day 2%; 1, 3-day 4% therapy as follows:

1. Patient No. 19 (study 92-11; 3-day 1% therapy) one day after the start of therapy patient reported vaginal odor.

2. Patient No. 42 (study 92-11; 3-day 1% therapy) reported vaginal burning 10 minutes after treatment on the first and second day of therapy.

3. Patient No. 80 (study 93-34; 3-day 1% therapy) pain with urination over excoriations.

4. Patient No. 187 (study 93-34; 3-day 1% therapy) vulvovaginal burning.

5. Patient No. 186 (study 93-34; 3-day 2% therapy) patient reported vulvovaginal itching which was worse in the morning.

6. Patient No. 198 (study 93-34; 3-day 2% therapy) reported vulvovaginal itching and burning.

7. Patient No. 89 (study 93-34; 3-day 4% therapy) vulvovaginal itching which increased after application of medication.

8. Patient No. 24 (study 93-34; 7-day 1% therapy) burning on urination after intercourse.

9. Patient No. 367 (study 93-40; 7-day 1% therapy) vaginal burning.

Treatment -related vulvovaginal adverse events, such as vaginal itching and burning, were reported by 45 women (15, 7-day 1% therapy; 13, 3-day 1% therapy; 12, 3-day 2% therapy; 4, 3-day 4% therapy; and 1, 500 mg single-dose vaginal tablet).

Safety Update: The sponsor submitted a safety update report on February 3, 2000 for the period 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 USA and Canada, or the 2% formulation marketed in Canada. For the same time frame the Schering-Plough Corporation reported eight ADRs for its Gyne-Lotrimin 3 Vaginal Cream, A product with the same active ingredient as Taro's product. Six of the eight ADRs were reported as treatment failures, one as making the condition worse and one as trauma to the vagina due to inserting the product too deep into the vagina. All reactions were reported as non-serious. For additional safety information, please refer to the safety review of Ling Chin, M. D. DOTCDP.

CONCLUSIONS

The results of the comparative, randomized, parallel group studies comparing the safety and efficacy of treatment with either a 2% clotrimazole vaginal cream for 3 days or a 1% clotrimazole vaginal cream for 7 days demonstrate:

1. That the 3-day 2% and 7-day 1% therapies were clinically, mycologically and therapeutically equivalent.

2. There appears to be no statistically significant difference between the 3-day 2% therapy and the 7-day 1% therapy.

3. The Taro 3-day 2% clotrimazole cream that has been marketed in Canada as a prescription product for 7 years and as an over-the-counter product for 2 years appears to be therapeutically equivalent to the Schering 3-day 2% which is currently marketed in the United States.

4. Shortening the duration of clotrimazole therapy from 7 to 3 days, and increasing the concentration of intravaginal clotrimazole from 1% to 2% had no effect on the incidence, nature or severity of adverse events.

5. The safety profiles of the 3-day 2% and the 7-day 1% therapies show no differences and there appears to be no safety issues with any of the cream formulations

Labeling: The sponsor submitted labeling amendments to this NDA on November 17, 1999, January 19, 2000 and February 3, 2000, for the carton, educational brochure and tube of their Clotrimazole Vaginal Cream 2%. A complete review of these amendments was done by Cheryl Turner, revised by the review teams [Division of Special Pathogens and Immunologic Drug Products (DSPIDP), Division of Over-the-Counter Products (DOTCDP) Division of Labeling and Non-Prescription Drug Compliance (DLNDC)] and forwarded to the sponsor for concurrence on March 13, 2000.

The trade name of "Trivagizole 3" that was suggested by the sponsor in its January 5, 2000 amendment has been reviewed in consultation with OPDRA (HFD-400). This amendment was acceptable to them.

RECOMMENDATION: The Applicant requests direct OTC approval for the use of Trivagizole 3 Clotrimazole Vaginal Cream USP, 2% for 3 days in treating patients with vulvovaginal candidiasis. Based on the results of clinical studies reviewed in NDA 20-574 and the fact that SPHCP has given Taro the right to reference all safety and efficacy data of NDA 20-574, I recommend approval of this NDA. The brand name of the product shall be "Trivagizole 3" and the labeling of the carton, educational brochure and tube should appropriately reflect the changes contained in the OTC labeling review of Cheryl Turner dated March 13, 2000.

/S/

Joseph K. Winfield, M. D.
Reviewing Medical Officer

Concurrence Only
HFD-590/Acting Div/Dir/RAlbrecht
3/28/00

cc: NDA 21-143
HFD-340
HFD-560/OTC
HFD-590
HFD-590/Dep/Dir/RAlbrecht
HFD-590/Team Leader/BLeissa 3/22/00
HFD-590/MO/JKWinfield
HFD-590/MO/ECox
HFD-590/PMO/CChi
HFD-725/Stat/LShen

APPEARS THIS WAY
ON ORIGINAL

MAR 2 0 2000

OTC Medical Officer's Review

NDA #: 21-143
Drug name (Generic Name): Clotrimazole Vaginal Cream 2%
Sponsor: Taro Pharmaceuticals
Pharmacologic Category: Vaginal Antifungal
Proposed Indication(s): Treat repeat vaginal yeast infections
Dosage Form and Route of Administration: Vaginal Cream applied via Reusable Applicator
Submission Date: February 3, 2000
CDER Date: February 4, 2000
Reviewer Name: Ling Chin
Review Date: February 5, 2000
CSO/PM Name: Dan Keravich

Material Reviewed
(1) Safety update report from Taro

Clinical Background

In 1999, Schering Plough Healthcare Products obtained approval for Gyne-Lotrimin 3 Vaginal Cream for OTC marketing. Approval was based on clinical trials conducted separately by Schering Plough and Taro, and a bridging study linking Taro's clotrimazole product to Schering Plough's clotrimazole product. Taro's and Schering's formulations of the 2% clotrimazole are essentially similar. Taro is now seeking approval to market their clotrimazole product independently. The same clinical trials are referenced and there is no additional efficacy data. As part of the NDA requirements, Taro was asked to provide a safety update. In a letter dated August 25, 1999, Taro reported that there is no additional safety information beyond that provided for the Gyne-Lotrimin 3 Vaginal Cream approval. In response to the request for further safety information, a safety update of the postmarketing experience of Gyne-Lotrimin 3 was submitted, and is the subject of this review.

Safety Update

The safety update is for the reporting period of June 15, 1999 to February 3, 2000. Taro stated that they have not received any reports of adverse reactions for their Clotrimazole Vaginal Cream 1% and 2%. Both formulations are marketed in Canada while only the 1% formulation is marketed in the U.S. There were 8 adverse events submitted to FDA by Schering Plough for their Gyne-Lotrimin 3 product, and these were obtained by Taro and submitted to FDA for this NDA review. Possibly because the postmarketing adverse event reports were of Schering's clotrimazole 3-day product, marketing data such as the number of units sold during the reporting period was not provided.

All 8 adverse events were non-serious. Six of the 8 were reports of an inadequate therapeutic response. In 1 of these 6 reports, the reporter stated that the yeast infection returned within 2 weeks.

Case 199-06-0172: Itching worsened with initial application of Gyne-Lotrimin 3. Consumer was seen in the emergency room and discharged with additional medication and instructions to continue using the product. Symptoms worsened and upon return to the emergency room, consumer was instructed to discontinue product use. Outcome was unknown.
Case 199-10-1477: Consumer reported deep insertion of the applicator into the vagina and subsequent trauma associated with her urethra and possibly bladder. The trauma was healing at the time of her report. No physician was seen.

Medical Officer Comments and Conclusions

The 8 adverse events submitted were all of a non-serious nature, and have been associated with all of the currently marketed OTC vaginal antifungal products, namely lack of effect, initial exacerbation of symptoms, and minor trauma with application.

There is no additional information submitted in this safety update that would preclude approval of this product.

/S/ 3/20/00
Ling Chin, M.D., M.P.H.
Medical Officer
DOCDP

/S/
Linda M. Katz, M.D., M.P.H.
Deputy Director 3/22/00
DOTCDP

APPEARS THIS WAY
ON ORIGINAL