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APPLICATION NUMBER: **20-574**

MEDICAL REVIEW(S)

NOV 10 1998

DATE SUBMITTED BY SPONSOR: NOVEMBER 25, 1997
DATE RECEIVED BY CDER: NOVEMBER 25, 1997
DATE RECEIVED BY REVIEWER: DECEMBER 9,1997
DATE REVIEW STARTED: JULY 1, 1998
DATE REVIEW COMPLETED: SEPTEMBER 21, 1998

MEDICAL OFFICER'S REVIEW OF NDA 20-574

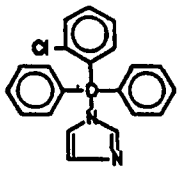
APPLICANT: Schering-Plough Healthcare Products
110 Allen Road
Liberty Corner, New Jersey 07938

GENERIC NAME: Clotrimazole 100 mg vaginal cream

TRADE NAME: Gyne-Lotrimin-3™ Vaginal Cream 2%

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: Gyne-Lotrimin-3™ Vaginal cream is indicated in the treatment of vulvovaginal 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] 20-525 [redacted]

NDA 20-574

MATERIAL REVIEWED: 76 Volumes

BACKGROUND

Vulvovaginal candidiasis (VVC) continues to be one of the most common gynecologic infections affecting women of the reproductive age group today. It is estimated that 75% of all women will have at least one episode of VVC during her lifetime. Although VVC is not a life threating disease, it can present distressing symptoms to the patient and can significantly decrease her quality of life. Therefore, the availability of safe and effective therapies that allow prompt treatment is much desired by the consumer.

Clotrimazole 1% vaginal cream is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic yeasts and is indicated for the treatment of vulvovaginal candidiasis. It was first approved by the FDA for use in the United States for the treatment of vulvovaginal candidiasis as a prescription product on November 8, 1978. Numerous prescription dosage strengths and forms have been approved for use in the US since that time.

In 1990 two sponsors of approved prescription antifungal azole products requested approval of their products for over-the-counter (OTC) use in treating VVC. The FDA considered these requests and in June, 1990 convened an Advisory Committee to determine if OTC marketing of these products were appropriate. Based on the long marketing history as to the safety and efficacy of these products in treating vulvovaginal candidiasis, the committee unanimously recommended that the imidazole class of vaginal antifungal therapies be approved for OTC use. The committee also recommended that only those products approved for 7-days of therapy in non-pregnant women with self recognizable, recurrent VVC which had been previously diagnosed by a physician be approved for OTC use. Therefore, on November 30, 1990, the FDA approved intravaginal clotrimazole 1% vaginal cream administered once daily for seven consecutive days as the first over-the-counter (OTC) vaginal antifungal.

Presently, the sponsor is of the opinion that a shorter course of therapy will improve compliance without compromising safety or efficacy and is requesting approval of a 3-day course of therapy of clotrimazole 2% vaginal cream for OTC use.

On March 10, 1992 representatives of the Division of Anti-Infective Drug Products (DAIDP), the Office of OTC Drug Evaluation of the Agency and the sponsor, Schering-Plough HealthCare Products, Inc. (SPHCP), met and agreed on a clinical program for the development of a 3-day clotrimazole cream therapy for the treatment of VVC. The program consisted of an initial dose ranging study in which three different clotrimazole concentrations would be evaluated, followed by two adequate and well-controlled studies to compare the 3-day therapies identified in the dose ranging study with 7-day 1% clotrimazole vaginal cream therapy. At this meeting it was also agreed that the studies could be investigator blinded and the primary efficacy end point would be the mycological cure.

The first two studies (protocols 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 for 7 days. The third study protocol (93-40) compared the 7-day 1% therapy and the 3-day 1% and 2% therapies.

Study 92-11 was terminated prematurely because of a high rate of negative vaginal cultures for *Candida* at study entry (51%) among patients with positive KOH wet mounts for *Candida* pseudohyphae. Study 93-34, which replaced study 92-11, was conducted in two parts at 22 investigational sites in the United States. In the first part, the 3-day 1%, 2% and 4% therapies and the 7-day 1% therapy were compared to determine the lowest concentration of clotrimazole used for 3 days which was at least as effective at the 7-day 1% therapy. An analysis of data from 96 patients enrolled in part 1 indicated that mycological and clinical cure rates were similar for all treatment groups. Therefore the sponsor decided to discontinue the study of the 4% product and part 2 of study compared the 3-day 1% and 2% therapies to the 7-day 1% therapy.

On November 29, 1993 in a teleconferences between the sponsor, SPHCP, and DAIDP of the FDA, an agreement was made that parts 1 and 2 of study 93-34 could be pooled and considered as a single study that compared the 3-day 1% and 2% clotrimazole vaginal cream to the 7-day 1% clotrimazole vaginal cream. It was also agreed that if equivalence is demonstrated, this combined study could possibly be utilized as one of the two pivotal studies required to support an NDA approval for a 3-day product.

Study 93-40 was conducted at 14 investigational sites in Canada and also compared the 3-day 1% and 2% therapies to the 7-day 1% therapy and would be considered the second pivotal study.

Each study was partially blinded in that patients were not aware of which 3-day therapy they were assigned. Patients with clinical signs and symptoms of vulvovaginal candidiasis were randomized and scheduled for follow-up evaluations at 14-17 and 28-31 days after the start of therapy.

After completing studies 93-34 and 93-40, SPHCP decided to seek approval of the 3-day 2% vaginal cream and filed NDA 20-574 on June 28, 1995 requesting approval for Gyne-Lotrimin 3™ 3-Day vaginal cream as an over-the-counter treatment of vulvovaginal candidiasis. A preliminary review of the data by the medical reviewer of the Division of Anti-Infective Drug Products (DAIDP) determined that only one of the submitted studies (93-40) possibly demonstrated equivalence of the 3-day 2% therapy to the 1% 7-day therapy while the other study (93-34) demonstrated equivalence of the 1% 3-day therapy to the 1% 7-day therapy and that neither of the 3-day products would meet DAIDP's two study "requirement" for approval of an OTC 3-day therapy. Based on this preliminary review, SPHCP withdrew NDA 20-574 on January 29, 1996.

The Sponsor met again with representatives of the Division of Anti-Infective Drug Products (DAIDP) on April 3, 1996 to discuss additional requirements that would be necessary to obtain approval for its 3-day 2% clotrimazole vaginal cream as an OTC product. At that meeting a protocol was design and agreed upon for the conduct of a future study that compared the 3-day 2% cream to the 7-day 1% cream It was also agreed that guidelines for the evaluation of study visits and the analyses and interpretation of study endpoints should be revised and that the data of studies 93-34 and 93-40 should be re-analyzed using the revised guidelines in order to obtain comparable results with the planned study.

Subsequent to this meeting, and before initiating the new study, SPHCP became aware of a clinical trial being conducted by Taro Pharmaceuticals, U.S.A., Inc. on a 3-day 2% clotrimazole cream which met the Agency's criteria that had be agreed upon in the April 3, 1996 meeting. The clinical trial design and evaluability criteria for the Taro study (protocol 95-50) had previously been reviewed and agreed upon by the Agency in a meeting with Taro on September 12, 1996. SPHCP acquired the rights to use the results of Taro's clinical study as the second pivotal efficacy trial needed for approval of the SPHCP 3-day 2% clotrimazole vaginal cream formulation.

On June 18, 1997, SPHCP and Taro held a joint pre-NDA meeting with the Division of Special Pathogen and Immunologic Drug Products (DSPIDP), a newly created Division in ODE-IV responsible for reviewing vaginal antifungals, and the Division of Over-the-Counter Drug Products. The following agreements were reached at that meeting:

- Schering studies (93-34 and 93-40) could be pooled and analyzed according to the revised guidelines of the 4/3/96 meeting and become the first of two studies.
- Taro's study (95-50) should be analyzed using the same FDA revised evaluability criteria to be applied to Schering's pooled study and could be used as the second pivotal study.
- The two companies were requested by the FDA to perform a "bridging" study that would demonstrate therapeutic equivalence between their respective formulations of the 2% clotrimazole vaginal creams when used for three days.

The Taro study (95-50) was conducted at 13 investigational sites in Canada. This study was an investigator blind, parallel group design with patients randomized equally into five treatment groups. Patients with a positive 10% KOH wet mount and a positive culture for *Candida* species were entered into the study with follow-up visits scheduled for 14-17 days and 35-42 days after the start of therapy.

On November 25, 1997, SPHCP resubmitted NDA 20-574 requesting approval to market the SPHCP 2% clotrimazole cream formulation over-the-counter for the 3-day treatment of vulvovaginal candidiasis. This resubmission includes the reanalysis of the results from the combined SPHCP studies, (93-34 and 93-40), and the Taro study (95-50) using the

criteria agreed upon at the April 3, 1996 meeting. These studies comprise the two pivotal clinical trials which SPHCP states support the safety and efficacy of a 3-day 2% clotrimazole cream OTC therapy for vulvovaginal candidiasis.

On January 8, 1998 SPHCP submitted an amendment to NDA 20-574 that included the final report of the "bridging" study (CTZ-9701) which compared the safety and therapeutic equivalence of the two formulations used in the NDA clinical trials. The results of these studies to support the sponsor's claim that 3-day 2% clotrimazole cream is equivalent to the currently approved 7-day 1% cream in treating VVC are presented in this medical officer's review.

RATIONALE FOR 3-DAY THERAPY

The sponsor states that the rationale for developing a 3-day therapy is based on the favorable USA marketing experience with the 7-day 1% clotrimazole cream (as a prescription and an OTC drug), as well as the favorable foreign marketing experience with the 3-day 2% clotrimazole cream. The principal benefit of the 3-day therapy, over the currently approved 7-day therapy of intravaginal 1% clotrimazole cream once-a-day for seven days, is increased convenience and greater patient compliance resulting from the reduced duration of therapy. This benefit would be available to patients without sacrificing either clinical or mycological efficacy or significantly increasing adverse events.

CLINICAL STUDIES

Three comparative studies (92-11, 93-34, 93-40) were initially conducted to evaluate the safety and efficacy of 3-day therapy with clotrimazole cream of different concentrations for the treatment of vulvovaginal candidiasis. Women with other infections and women who failed to meet all other study entry criteria were excluded from the studies. Eligible patients were randomly assigned, in equal numbers, to each treatment. The first and second studies (protocols 92-11 and 93-34 compared 1%,2% and 4% clotrimazole cream used for 3 days to 1% clotrimazole cream used for 7 days. The third study (protocol 93-40) compared the 7-day 1% therapy and the 3-day 1% and 2% therapies.

Study 92-11 was terminated prematurely because of a high rate of negative vaginal cultures for *Candida* at study entry (51%) among patients with positive KOH wet mounts, and a resulting concern about investigator experience. This study will not analyzed for efficacy but will be included in the safety data analyses. Studies 93-34 and 93-40 included non-pregnant patients who had not had an episode of vulvovaginal candidiasis in the 60 days before study entry. Before the start of therapy patients had vaginal smears cultured for *Candida* with a determination of the species, and were required to have 10% KOH wet mount mounts of vaginal smears that were positive for *Candida* pseudohyphae and have at least one clinical sign or symptom of vulvovaginal candidiasis. Patients were scheduled for follow-up evaluations at 14-17 and 28-31 days

Efficacy analyses for all studies used the revised criteria and included only those patients who satisfied all of the following:

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 following definitions of mycological, clinical and therapeutic cure were used (based on discussions and agreements on revised criteria for "cure" and "fail" between SPHCP and the Agency on April 3, 1996):

Mycological Cure: Patient had a negative KOH wet mount for *Candida* pseudohyphae and a negative culture for *Candida* at visits 2 and 3. (if there is a disagreement between the wet mount and culture results, the culture result will be used. If a culture is missing, the wet mount result will be used.)

Clinical Cure: Patient had "improved signs and symptoms" at visit 2 and no symptoms at visit 3 other than "mild" itching which is not considered a clinical failure. Symptoms include itching/irritation (a single symptom) and burning. Signs include erythema, edema, excoriations. Vaginal discharge is not included as a sign as it is too prevalent and difficult to subjectively quantitate.

"Improved signs and symptoms" was defined as a reduction in the mean severity score of all signs and symptoms recorded as visit 1. If the severity score of a sign/symptom recorded, that sign/symptom was not used in the determination of the mean score at that time point only. If the patient's mean sign/symptom score at visit 2 was equal to or greater than her mean score at visit 1, the patient was counted as a clinical failure.

Therapeutic Cure: Patient had both a clinical and mycological cure. If a patient was mycological and/or a clinical failure, she was counted as a therapeutic failure.

Mycological Relapse: Patient had a negative culture for *Candida* at visit 2, but had a positive culture at visit 3. (if culture was missing, KOH results will be used).

The primary efficacy variable based on the revised criteria is the therapeutic cure. Clinical and mycological cure rates, mycological relapse rates, and changes in the severity scores of signs and symptoms of candidiasis were secondary efficacy variables.

Although the formulation used in SPHCP'S and TARO's clinical studies were qualitatively and quantitatively very similar, at the June 18, 1997 pre-NDA meeting between Taro, SPHCP, the Division of Special Pathogens and Immulogic Drug Products (DSPIDP), and the Division of Over-the-Counter Products (OTC), a "bridging" study was recommended so that clinical equivalence between the two formulations could be demonstrated. The sponsors conducted study CTZ 97-01 in order to satisfy this request and to support the use of these two formulations for a single NDA which will seek approval of Schering's formulation.

Reviewer's Comment: As noted in the clinical studies and background sections of this review, agreements between the sponsors and the FDA defining criteria that would be utilized in evaluating the efficacy and safety of the 3-day 2% clotrimazole vaginal cream when compared to the 7-day 1% clotrimazole cream were made through many meetings and teleconferences. Data that have been submitted by the sponsors (Schering and Taro) for each of the clinical studies conducted for this NDA have been carefully reviewed and verified by the FDA medical reviewer. The number of patients found to be evaluable and the primary efficacy endpoint (therapeutic cure) obtained in studies 95-50 and 97-01 are the same as those submitted by the sponsors. The number of patients considered as evaluable and assessed as cures in studies 93-34 and 93-40 are those of the FDA medical reviewer. These differ from those submitted by the sponsor because in the medical officer's evaluation of the data, a significant number of patients had been excluded from the efficacy analyses by the sponsor because of "missing data at final visit". These patients are considered as evaluable by the medical reviewer because most of the patients have a positive fungal culture at visit 2 and should have been considered as mycological failures at visit 2 and therefore therapeutic failures at visit 3. All patients have been discussed with the sponsor who agree with the results obtained by the medical reviewer. All safety data for each study was provided by the sponsors and accepted by the medical officer.

Efficacy and safety data for each clinical study will be presented in the results section of this review followed by an NDA summary.

Results

Study 93-34

Title: A comparison of the safety and efficacy of 3-day versus 7-day therapy with various doses of clotrimazole cream in the treatment of vulvovaginal candidiasis.

Study Objectives: The study was conducted to evaluate 1%, 2%, and 4% intravaginal clotrimazole cream used once daily for 3 consecutive days and 1% intravaginal clotrimazole cream used once daily for 7 consecutive days for the treatment of vulvovaginal candidiasis. The study was conducted in two parts. The first objective of part 1 was to determine the lowest concentration of clotrimazole used for 3 days which was at least as effective as the 7-day therapy. The objective of part 2 of the study was to provide additional data on the comparative safety and efficacy of the 3-day therapy identified in the first part of the study and the 7-day therapy.

Study Design: A blinded analyses of data from 96 patients enrolled in Part 1 indicated that mycological and clinical cure rates were similar for all treatment regimens. Because there appeared to be no benefit to the 3-day 4% therapy, the sponsor elected to discontinue further enrollment of patients in the 3-day 4% group. In parts 1 and 2 of the study, identical procedures were followed for enrolling, evaluating and following-up patients. Patients with at least one clinical sign or symptom of vulvovaginal candidiasis and a positive 10% KOH wet mount for *Candida* pseudohyphae, who satisfied all other study inclusion and exclusion criteria were selected to participate in the study.

In Part 1 of the study, patients were randomized in equal numbers in blocks of 4 to once daily treatment with intravaginal 1% (50 mg/day), 2% (100 mg/day) or 4% (200 mg/day) clotrimazole cream for 3 consecutive days or to a once daily treatment with intravaginal 1% (50 mg/day) clotrimazole cream for 7 consecutive days. In Part 2, patients were randomized in equal numbers in blocks of 3 to treatment with either 1% or 2% clotrimazole cream for 3 days or 1% clotrimazole cream for 7 days.

Patients were instructed to take their assigned treatment at bedtime, starting on the day they enrolled in the study. Patients were provided with diary cards on which they recorded symptoms of their VVC immediately before taking each dose of study drug.

Patients were scheduled to return for follow-up evaluations at 14-17 days (visit 2) and 28-31 days (visit 3) after the start of therapy. At visit 2, patients returned their completed diary cards and had the panel of laboratory safety tests and a serum pregnancy test repeated. At each visit, patient had vaginal examinations performed and their clinical signs and symptoms were recorded. Vaginal secretion specimens were obtained for evaluation in a 10% KOH wet mount and by culture for *Candida albicans, Candida glabrata, Candida parapsilosis,* and *Candida tropicalis.*

At each follow-up visit, patients were questioned about the occurrence of adverse experiences and the use of any medications since the time of their last visit.

DEMOGRAPHICS

A total of 268 patients was enrolled and randomized in parts 1 and 2, 131 in the 3-day 2% clotrimazole group and 137 in the 1% 7-day treatment group. There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, weight and height). Most patients were White (78%), were less than 35 years of age (68%), and had been previously treated for vulvovaginal candidiasis (64%). The mean age of all patients was 31.5 years, and their ages ranged from 18 to 80 years. Patients who received drug were included in the analyses and their baseline characteristics are shown in Table 1.

Table 1
Clotrimazole Protocol 93-34
Baseline Information, All Patients

	3 DAY 2%	7 DAY 1%
NUMBER OF PATIENTS	131	137
AGE CATEGORY		
≤24	51 (38.9%)	55 (40.1%)
25-34	38 (29.0%)	38 (27.2%)
35-44	25 (19.1%)	28 (20.4%)
≥45	17 (13.0%)	16 (11.7%)
AGE (YRS)		
MEAN	31.40	30.70
SEM	1.05	0.92
RANGE	18-80	18-67
N	131	137
WEIGHT (LBS)		
MEAN	148.72	149.21
SEM	3.18	3.12
RANGE	99-288	99-338
N	130	137
HEIGHT (IN)		
MEAN	64.94	65.16
SEM	0.22	0.23
RANGE	57-72	59-71
N	130	137
RACE		
BLACK	24 (18.3%)	21 (15.3%)
OTHER	6 (4.6%)	7 (5.1%)
WHITE	101(77.1%)	109 (79.6%)
PRIOR CANDIDIASIS		
FIRST TIME	36 (27.5%)	48 (35.0%)
RECURRENT	88 (67.2%)	83 (60.6%)
UNKNOWN	7 (5.3%)	6 (4.4%)

Investigators

Twenty-two principal investigators from various locations in the United States participated in the study. Their CVs have been reviewed and each is considered well qualified to conduct the study. The names and location of the principal investigators and the number of enrolled and evaluable patients for each treatment group are listed in Table 2.

Table 2
Clotrimazole Protocol 93-34
Enrolled and Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY ENROLLED	EVALUABLE (%)	CLOTRIMAZOLE 1% 7-DAY ENROLLED	EVALUABLE (%)
Appel, Theodore B., M.D. Boulder, Colorado	8	8 (100)	8	8 (100)
Bame, Marvin L., M. D. Vancover, Washington	1	1 (100)	1	1 (100)
Basiliere, Eugene J., M. D. Chula Vista, California	10	10 (100)	12	10 (83)
Cohen, Mark P., M. D. Birmingham, Alabama	1	1 (100)	2	1 (50)
Davis, Dean E., M. D. Spartansburg, South Carolina	6	6 (100)	7	5 (71)
Dingfelder, James R. , M. D. Chapel Hill, North Carolina	3	3 (100)	3	3 (100)
Drehobl, Margaret, M. D. San Diego, California	1	1 (100)	2	2 (100)
Giesler, Carl F., M. D. Houston, Texas	1	1 (100)	1	0 (0)
Harris, John W., M. D. Murray, Utah	4	3 (75)	4	3 (75)
Iravani, Abdollah, M. D. Orlando, Florida	16	15 (94)	16	15 (94)
Joseph, Marilyn S. / Brooker, Doris, M. D. Minneapolis, Minnesota	18	14 (78)	18	18 (100)
Kapernick, Peter, M. D./Brooker, Doris,M.D. Minneapolis, Minnesota	13	12 (93)	13	10 (77)
Kassman, Neil, M. D. Statesville, North Carolina	5	5 (100)	4	0 (0)
Leib, Luis, M. D. Dallas, Texas	1	1 (100)	2	2 (100)
Milas, John, M. D. Greer, South Carolina	7	7 (100)	6	6 (100)
Nevel, Etta, M. D. South Bend, Indiana	4	2 (50)	6	5 (83)
Saier, Fulton L., M. D. Portland, Oregon	1	1 (100)	1	0 (0)
Soltes, Barbara, M. D./ Lisa, Edward, M. D. Chicago, Illinois	8	6 (75)	8	6 (75)
Spellacy, William N., M. D. Tampa, Florida	2	1 (50)	2	2 (100)
Stoltz, Randall R., M. D. Evansville, Indiana	8	8 (100)	8	8 (100)
Stump, Charles A., M. D. Daytona Beach, Florida	0	0 (0)	1	0 (0)
Young, Ronald L., M. D. Houston, Texas	13	3 (23)	12	4 (33)
TOTAL	131	109 (83)	137	109 (80)

Disposition

The disposition of all patients that were enrolled in study 93-34 and were eligible for evaluation for efficacy and safety is shown in Table 3 below.

Table 3
Clotrimazole Protocol 93-34
Disposition of Patients

	Clotrimazole 3-Day 2%	Clotrimazole 7-Day 1%
Randomized to Treatment	131	137
Treated	131	137
Evaluable for Efficacy	109	109
Non-Evaluable for Efficacy	22	28
Negative baseline mycology	19	20
No follow-up data after baseline	3	8
Total Safety Evaluable Population	131	137

The number of evaluable patients that were considered as cured by the applicant and the medical officer by investigator for patients in study 93-34 is shown in Table 4.

Table 4
Clotrimazole Protocol 93-34
Therapeutic Cure Rates of Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY EVALUABLE	CURED (%)	CLOTRIMAZOLE 1% 7-DAY EVALUABLE	CURED (%)
Appel, Theodore B., M.D. Boulder, Colorado	8	6 (75)	8	2 (25)
Bame, Marvin L., M. D. Vancover, Washington	1	1 (100)	1	1 (100)
Basiliere, Eugene J., M. D. Chula Vista, California	10	5 (50)	10	6(60)
Cohen, Mark P., M. D. Birmingham, Alabama	1	1 (100)	1	0 (0)
Davis, Dean E., M. D. Spartansburg, South Carolina	6	1 (17)	5	1 (20)
Dingfelder, James R., M. D. Chapel Hill, North Carolina	3	1 (33)	3	0 (0)
Drehobl, Margaret, M. D. San Diego, California	1	0 (0)	2	2 (100)
Giesler, Carl F., M. D. Houston, Texas	1	1 (100)	0	0 (0)
Harris, John W., M. D. Murray, Utah	3	0 (0)	3	1 (33)
Iravani, Abdollah, M. D. Orlando, Florida	15	7 (47)	15	7 (47)
Joseph, Marilyn S. / Brooker, Doris, M. D. Minneapolis, Minnesota	14	7 (50)	18	10 (56)
Kapernick, Peter, M. D./Brooker, Doris,M.D. Minneapolis, Minnesota	12	7 (58)	10	2 (20)
Kassman, Neil, M. D. Statesville, North Carolina	5	3 (60)	0	0 (0)
Leib, Luis, M. D. Dallas, Texas	1	0 (0)	2	2 (100)
Milas, John, M. D. Greer, South Carolina	7	3 (43)	6	3 (50)
Nevel, Etta, M. D. South Bend, Indiana	2	1 (50)	5	2 (40)
Saier, Fulton L., M. D. Portland, Oregon	1	0 (0)	0	0 (0)
Soltes, Barbara, M. D./ Linn, Edward, M. D. Chicago, Illinois	6	3 (50)	6	3 (50)
Spellacy, William N., M. D. Tampa, Florida	1	0 (0)	2	0 (0)
Stoltz, Randall R., M. D. Evansville, Indiana	8	3 (38)	8	5 (63)
Stump, Charles A., M. D. Daytona Beach, Florida	0	0 (0)	0	0 (0)
Young, Ronald L., M. D. Houston, Texas	3	2 (67)	4	2 (50)
TOTAL	109	52 (48)	109	49 (45)

Efficacy

Given in Table 5 are the clinical, mycological and therapeutic cure rates obtained in the study for each treatment group.

Table 5
Study 93-34
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	CLOTRIMAZOLE 2% 3-DAY	CLOTRIMAZOLE 1% 7-DAY	1% 7-DAY VS 2% 3-DAY 95% CI
Clinical Cure	88/109 (81%)	93/109 (85%)	-6, 18
Mycological Cure	57/109 (52%)	53/109 (49%)	-10, 18
Therapeutic Cure	52/109 (48%)	49/109 (45%)	-11, 17

APPEARS THIS WAY
ON ORIGINAL

Safety

The twenty-two investigators in the United States enrolled 454 patients (137, 7-day, 1% therapy; 138, 3-day 1%; 131, 3-day 2%; 48, 3-day 4% therapy) who used at least one dose of their assigned treatment and are included in the safety analyses of this study. The safety profiles for the 7-day and each of the 3-day therapies were not statistically different. The number of adverse events reported regardless of causality for each treatment regimen is listed in Table 6 below:

Table 6
Clotrimazole Protocol 93-34
Incidence and Severity of Adverse Events

Treatment	Total # Patients	# Patients w/Event	# of Events	Severity		
				Mild	Moderate	Severe
1% 7 Day	137	47 (34%)	96	59 (61%)	34 (35%)	2 (3%)
1% 3 Day	138	54 (39%)	116	53 (46%)	51 (44%)	10 (9%)
2% 3 Day	131	39 (30%)	75	40 (53%)	25 (33%)	10 (13%)
4% 3 Day	48	20 (42%)	47	22 (47%)	20 (43%)	5 (11%)

Adverse Events

One patient discontinued treatment because of an adverse event. Patient No. 459 (7-day 1% therapy) did not take her first dose of study drug until day 9 after it was dispensed to her. The patient reported spotting after her first dose of clotrimazole and discontinued further use of the drug. The investigator recorded "protocol violation" as the reason the patient discontinued therapy, and not a discontinuation due to an adverse event.

Four patients were discontinued from the study at their first follow-up evaluation because of adverse events:

1. Patient No. 42 (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 (7-day 1% therapy) had otitis media with onset on the fifth day of therapy.

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

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

Adverse events, regardless of causality, were reported by 46 (34%) patients receiving 7-day 1% therapy, 54 (39%) receiving 3-day 1% therapy, 39 (30%) receiving 3-day 2% therapy, and 20 (42%) receiving 3-day 4% therapy (Table 6).

Adverse events which were possible, probably, or definitely related to treatment (i.e., treatment-related) were reported by 12 (9%) patients receiving 7-day 1% therapy, 13 (9%) receiving 3-day 1% therapy, 11 (8%) receiving 3-day 2% therapy, and 6 (13%) receiving 3-day 4% therapy (Table 7).

The following seven treatment-related adverse events were judged by the investigators to be severe: pain on urination (7-day 1% therapy); pain on urination over excoriations, vulvovaginal burning (3-day 1% therapy); vulvovaginal itching (2 cases), vulvovaginal burning (3-day 2% therapy); vulvovaginal itching (3-day 4% therapy).

Table 7
Clotrimazole Protocol 93-34
Incidence and Severity of Adverse Events
Possibly, Probably or Definitely Related to Treatment

Event	Treatment	Total # Patients	# Patients w/Event	# of Events	Severity -Mild	Severity Moderate	Severity Severe
TOTAL	1% 7 DAY	137	12 (9%)	20	10 (50%)	9 (45%)	1 (5%)
	1% 3 DAY	138	13 (9%)	20	11 (55%)	7 (35%)	2 (10%)
	2% 3 DAY	131	11(8%)	13	4 (31%)	6 (46%)	3 (23%)
	4% 3 DAY	48	6 (13%)	10	5 (50%)	4 (40%)	1 (10%)
PRURITUS GENITAL	1% 7 DAY	137	1 (1%)	1	1 (100%)	0	0
	1% 3 DAY	138	2 (1%)	2	1 (50%)	1(50%)	0
	2% 3 DAY	131	2 (2%)	2	0	0	2 (100%)
	4% 3 DAY	48	1 (2%)	1	0	0	1 (100%)
RASH	2% 3 DAY	131	1 (1%)	1	0	1 (100%)	0
SKIN DISORDER	1% 3 DAY	138	2 (1%)	2	0	1 (50%)	1 (50%)
MYALGIA	1% 3 DAY	138	1 (1%)	1	1 (100%)	0	0
DYSPAREUNIA	1% 7 DAY	137	2 (1%)	2	1 (50%)	1 (50%)	0
ABDOMINAL PAIN	1% 7 DAY	137	1 (1%)	1	0	1 (100%)	0
STOOL ABNORMAL	1% 3 DAY	138	1 (1%)	1	1 (100%)	0	0
SGPT INCREASED	1% 3 DAY	138	1 (1%)	1	1 (100%)	0	0
ANEMIA	1% 7 DAY	137	1 (1%)	1	1 (100%)	0	0
DYSURIA	1% 7 DAY	137	3 (2%)	3	1 (100%)	0	0
	4% 3 DAY	48	1 (2%)	1	1 (100%)	0	0
URINARY FREQ	1% 3 DAY	138	1 (1%)	1	0	1 (100%)	0
	4% 3 DAY	48	1 (2%)	1	1 (100%)	0	0
UTI	1% 3 DAY	138	1 (1%)	1	0	1 (100%)	0
	2% 3 DAY	131	2 (2%)	2	0	2 (100%)	0
DYSMENORRHEA	1% 7DAY	137	1 (1%)	1	0	1 (100%)	0
LEUKORRHEA	1% 7 DAY	137	1 (1%)	1	0	1 (100%)	0
	2% 3 DAY	131	1 (1%)	1	0	1 (100%)	0
	4% 3 DAY	48	2(4%)	2	1 (50%)	1 (50%)	0
VAGINAL DRYNESS	1% 3 DAY	138	1 (1%)	1	1 (100%)	0	0
VAG BLEEDING	1% 2 DAY	137	1 (1%)	1	1 (100%)	0	0
VAGINITIS	1% 7 DAY	137	7 (5%)	9	4 (44%)	5 (56%)	0
	1% 3 DAY	138	5 (4%)	9	5 (56%)	3 (33%)	1 (11%)
	2% 3 DAY	131	5 (4%)	5	2 (40%)	2 (40%)	1 (20%)
	4% 3 DAY	48	2 (4%)	2	1 (50%)	1 (50%)	0
TUMOR, BENIGN	4% 3 DAY	48	1 (2%)	1	0	1(100%)	0
HEADACHE	2% 3 DAY	131	1 (1%)	1	1 (100%)	0	0
ABNORMAL LAB	4% 3 DAY	48	1 (2%)	1	1 (100%)	0	0
PAIN	2% 3 DAY	131	1 (1%)	1	1 (100%)	0	0
LOCAL REACTION	1% 3 DAY	138	1 (1%)	1	1(100%)	0	0
	4% 3 DAY	48	1 (2%)	1	0	1 (100%)	0

Summary and Conclusion Protocol 93-34

Four hundred fifty-four patients with clinical evidence of vaginal candidiasis were assigned to treatment, and 137 of them were treated with 1 % clotrimazole vaginal cream for 7 days, and 317 were treated with clotrimazole vaginal cream for 3 days (138, 1% cream; 131, 2% cream; 48, 4% cream). The 7-day 1% therapy is approved for over-the-counter use.

A blinded analyses of data from the first 96 patients enrolled in the study indicated that mycological and clinical cure rates were very similar for all treatment groups and because there appeared to be no benefits to the 3-day 4% therapy, the Sponsor elected to discontinue further enrollment of patients in the 3-day 4% group.

The most frequent reason for excluding patients from the efficacy analyses was a negative culture for *Candida* at study entry (approximately 15%). In comparisons of the 3-day 2% therapy and the 7-day 1% therapy for clinical, mycological and therapeutic cures, there were no statistically significant differences between the two treatment groups. Clinical, mycological and therapeutic cure rates were 81%, 52% and 48% respectively for the 3-day 2% therapy and 85%, 49% and 45% for the 7-day 1% therapy.

Adverse events which were possibly, probably or definitely related to treatment were reported for 11 (8%) patients treated for 3-days with 2% clotrimazole and 12 (9%) patients treated for 7 days with 1% clotrimazole.

The results of the study show that the 3-day therapy with 2% clotrimazole cream is equivalent in efficacy and safety to the 7-day 1% therapy in patients with vulvovaginal candidiasis.

Study 93-40

Title: An open, parallel study to compare the efficacy of two 3-day therapies versus 7-day therapy with clotrimazole cream in the treatment of vulvovaginal candidiasis.

Study Objectives: The study was conducted to evaluate 1% and 2% intravaginal clotrimazole cream used once daily for 3 consecutive days and 1% intravaginal clotrimazole cream used once daily for 7 consecutive days for the treatment of vulvovaginal candidiasis.

Study Design: Patients with al least one clinical sign or symptom of vulvovaginal candidiasis and a positive 10% KOH wet mount for *candida* pseudohyphae, who satisfied all other study inclusion and exclusion criteria were selected to participate in the study. After giving their written consent, patients had: a medical history taken; physical, pelvic, and vaginal examinations; a panel of routine laboratory safety tests performed; a Papanicolaou smear if one had not been performed within the prior year; a saline wet mount screed for clue cells, leukocytes and trichomonads; and vaginal smears taken for culture for Trichomonas, *Candida albicans, Candida glabrata, Candida parapsilosis,* and *Candida* tropicalis and for microscopic examination in a 10% KOH wet mount for *Candida* pseudohyphae. Patients of child-bearing potential had rapid urine and serum pregnancy tests performed.

Patients were randomized in equal numbers in blocks of 6 to once daily treatment with intravaginal 1% (50 mg/day) or 2% (100 mg/day) cream for 3 consecutive days or to a once daily treatment with intravaginal 1% (50 mg/day) clotrimazole cream for 7 consecutive days. Study drugs supplies were packaged in identical boxes containing either three or seven clotrimazole applicators, and either one 2 g tube of clotrimazole for the 3-day treatments or one 45 g tube for the 7-day treatment. Since the tubes of clotrimazole cream for the 3 day treatments were identical in appearance, patients assigned to 3-day clotrimazole therapy were blinded as to the particular 3-day therapy they received.

Patients were instructed to take their assigned treatment at bedtime, starting on the day they enrolled in the study. Patients were provided with diary cards on which they recorded symptoms of their VVC immediately before taking each dose of study drug.

Patients were scheduled to return for follow-up evaluations at 14-17 days (visit 2) and 28-31 days (visit 3) after the start of therapy. At visit 2, patients returned their completed diary cards and had the panel of laboratory safety tests and a serum pregnancy test repeated. At each visit, patients had vaginal examinations performed and their clinical signs and symptoms were recorded. Vaginal secretion specimens were obtained for evaluation in a 10% KOH wet mount and cultured for *Candida albicans, Candida glabrata, Candida parapsilosis,* and *Candida tropicalis.*

At each follow-up visit, patients were questioned about the occurrence of adverse experiences and the use of any medications since the time of their last visit.

DEMOGRAPHICS

A total of 262 patients was enrolled and randomized, 131 in each clotrimazole treatment group (3-day 2% and 7-day 1%). There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, weight and height. Most patients were White (90 %), were less that 35 (47 %) and had previously been treated for vulvovaginal candidiasis (75 %). Patients who received any drug were included in the analyses and their baseline characteristics are listed in the Table 8.

Table 8
Clotrimazole Protocol 93-40
Baseline Information, All Patients

	3 DAY 2%	7 DAY 1%
NUMBER OF PATIENTS	131	131
AGE CATEGORY		
≤24	38 (29.0%)	33 (25.2%)
25-34	51 (38.9%)	52 (39.7%)
35-44	24 (18.3%)	29 (22.1%)
≥45	18 (13.7%)	17 (13.0%)
AGE (YRS)		
MEAN	32.38	32.05
SEM	1.01	0.83
RANGE	18-73	18-57
N	131	131
WEIGHT (LBS)		
MEAN	137.13	137.70
SEM	2.56	2.67
RANGE	85-251	76-260
N	130	131
HEIGHT (IN)		
MEAN	64.32	64.95
SEM	0.24	0.21
RANGE	57-71	60-71
N	131	131
RACE		
BLACK	6 (4.6%)	8 (6.1%)
OTHER	7 (5.3%)	6 (4.6%)
WHITE	118(90.1%)	117 (89.3%)
PRIOR CANDIDIASIS		
NO	32 (24.4%)	35 (26.7%)
YES	99 (75.6%)	96 (73.3%)

Investigators

Fourteen principal investigators from various locations in Canada participated in the study. Their CVs have been reviewed and each is considered well qualified to conduct the study. The names and location of the principal investigators and the number of enrolled and evaluable patients for each treatment group are listed in Table 9.

Table 9
Clotrimazole Protocol 93-40
Enrolled and Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY ENROLLED	EVALUABLE (%)	CLOTRIMAZOLE 1% 7-DAY ENROLLED	EVALUABLE (%)
Achyuthan, Geeta, M. D. Regina, SASK, Canada	16	16 (100)	16	15 (94)
Bell, Alan, M. D., Downsview, ON, Canada	16	14 (88)	16	14 (88)
Choquette, Pierre, M. D. Chomedy, Laval, QC, Canada	8	8 (100)	9	9 (100)
Cote,ichel, M. D. Sherbrooke, QC, Canada	4	4 (100)	4	4 (100)
Gemayel, Kange, M. D. Montreal, QC. Canada	10	8 (80)	10	8 (80)
Graham, John, M. D. Halifax, NS, Canada	8	3 (38)	9	4 (44)
Lavoie, Henri, M. D. Montreal, QC, Canada	11	10 (91)	11	11 (100)
Malouf, Maan Montreal, QC, Canada	4	4 (100)	3	2 (67)
Mansour, Nabil, M. D. Greenfield Park, QC, Canada	12	11 (92)	12	12 (100)
Martel, Alain, M. D. Ste-Foy,QC, Canada	3	3 (100)	3	3 (100)
Namis, Nabil, M.D. Guelph, ON, Canada	12	9 (75)	12	9 (75)
Shore, Melvin, M. D. Montreal, QC, Canada	7	7 (100)	7	7 (100)
Sidani, Paul, M. D. Montreal, Canada	14	10 (71)	14	7 (50)
Whitsitt, Paul, M. D, Oshawa, ON, Canada	6	3 (50)	5	3 (60)
Total	131	110 (84)	131	108 (82)

Disposition

The disposition of all patients that were enrolled in study 93-40 and were eligible for evaluation for efficacy and safety is shown in Table 10 below.

Table 10
Clotrimazole Protocol 93-40
Disposition of Patients

	Clotrimazole 3-Day 2%	Clotrimazole 7-Day 1%
Randomized to Treatment	131	131
Treated	131	131
Evaluable for Efficacy	110	108
Non-Evaluable for Efficacy	21	23
Negative baseline mycology	16	20
No follow-up data after baseline	4	2
No follow-up culture after baseline	1	1
Total Safety Evaluable Population	131	131

The number of evaluable patients that were classified as therapeutic cures is shown in Table 11 below.

Table 11
Clotrimazole Protocol 93-40
Therapeutic Cures of Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY EVALUABLE	CURED (%)	CLOTRIMAZOLE 1% 7-DAY EVALUABLE	CURED (%)
Achyuthan, Geeta, M. D. Regina, SASK, Canada	16	7 (44)	15	10 (67)
Bell, Alan, M. D., Downsview, ON, Canada	14	3 (21)	14	7 (50)
Choquette, Pierre, M. D. Chomedy, Laval, QC, Canada	8	5 (63)	9	6 (67)
Cote,ichel, M. D. Sherbrooke, QC, Canada	4	2 (50)	4	3 (75)
Gemayel, Kange, M. D. Montreal, QC. Canada	8	4 (50)	8	3 (38)
Graham, John, M. D. Halifax, NS, Canada	3	0 (0)	4	3 (75)
Lavoie, Henri, M. D. Montreal, QC, Canada	10	5 (50)	11	4 (36)
Malouf, Maan Montreal, QC, Canada	4	3 (75)	2	1 (50)
Mansour, Nabil, M. D. Greenfield Park, QC, Canada	11	6 (55)	12	5(42)
Martel, Alain, M. D. Ste-Foy,QC, Canada	3	0 (0)	3	3 (100)
Namis, Nabil, M.D. Guelph, ON, Canada	9	6 (67)	9	5 (56)
Shore, Melvin, M. D. Montreal, QC, Canada	7	3 (43)	7	2 (29)
Sidani, Paul, M. D. Montreal, Canada	10	4 (40)	7	5 (86)
Whitsitt, Paul, M. D, Oshawa, ON, Canada	3	3 (100)	3	2 (67)
Total	110	51 (46)	108	60 (56)

Efficacy

Given in Table 12 are the clinical, mycological and therapeutic cure rates obtained in the study.

Table 12
Study 93-40
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	CLOTRIMAZOLE 2% 3-DAY	CLOTRIMAZOLE 1% 7-DAY	1% 7-DAY VS 2% 3-DAY 95% CI
Clinical Cure	100/110 (91%)	100/108 (93%)	-10, 7
Mycological Cure	52/110 (47%)	62/108 (57%)	-24, 4
Therapeutic Cure	51/110 (46%)	60/108 (56%)	- 23, 5

Safety

The safety profiles for the 7-day and each of the 3-day therapies were not different and there were no safety issues.

Adverse Events

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 (7-day 1% therapy) was hospitalized for a bilateral thoracic sympathectomy 21 days after the start of therapy

2. Patient No.477 (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 the pregnancy was provided by the investigator.

Two patients were discontinued from the study at their first follow-up evaluation because of adverse events:

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

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

Adverse events, regardless of causality were reported by 14 (11%) patients receiving 7-day therapy, 17 (13%) receiving 3-day 1% therapy, and 18 (14%) receiving 3-day 2% therapy. (Table 13).

Adverse events which possibly, probably or definitely related to treatment (i. e., treatment-related) were reported by 2 (2%) patients receiving 7-day 1% therapy, none receiving 3-day 1% therapy, and 1 (1%) receiving 3-day 2% therapy (Table 14).

The only adverse event that was judged to be severe and treatment related was one case of vaginal burning (patient No. 367; 7-day 1% therapy). Other treatment-related vulvovaginal adverse events were reported by 2 patients (1, 7-day 1% therapy; 1, 3-day 2% therapy).

Table 13
Clotrimazole Protocol 93-40
Incidence and Severity of Adverse Events

Treatment	Total # Patients	# Patients w/Event	# of Events	Severity: Mild	Severity: Moderate	Severity: Severe
1% 7 Day	131	14 (11%)	21	9 (43%)	11 (52%)	1 (5%)
1% 3 Day	133	17 (13%)	27	13 (48%)	10 (37%)	4 (5%)
2% 3 Day	131	18 (14%)	28	10 (36%)	13 (46%)	5 (18%)

Table 14
Clotrimazole Protocol 93-40
Incidence and Severity of Adverse Events
Possibly, Probably, or Definitely Related to Treatment

Event	Treatment	Total # Patients	# Patients w/Event	# of Events	Severity: Mild	Severity: Moderate	Severity: Severe
TOTAL	1% 7 Day	131	2 (2.0%)	3	1 (33.0%)	1 (33.0%)	1 (33.0%)
	1% 3 Day	133	0	0	0	0	0
	2% 3 Day	131	1 (1.0%)	3	1 (33.3%)	2 (67.0%)	0
PRURITUS	2% 3 Day	131	1 (1.0%)	1	0	1 (100%)	0
RASH	2% 3 Day	131	1 (1.0%)	1	0	1 (100%)	0
EDEMA	2% 3 Day	131	1 (1.0%)	1	1 (100%)	0	0
APPLICATION SITE REACTION	1% 7 Day	131	1 (1.0%)	1	0	1 (100%)	0
APPLICATION SITE, BURNING	1% 7 Day	131	2 (2.0%)	2	1 (50.0%)	0	1 (50/0%)

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Summary Study 93-40

Two hundred sixty-two patients with clinical evidence of vulvovaginal candidiasis were randomly and equally (131/group) assigned to receive either 1% clotrimazole vaginal cream for 7 days or 2% clotrimazole vaginal cream for 3 consecutive days. Clinical mycological and therapeutic cure rates were 93%, 57% and 56%, respectively for the 7-day 1% therapy and 91%, 47% and 46% respectively for the 3-day 2% therapy.

No patient discontinued therapy because of an adverse event. Serious adverse events were reported for two patients. Both events involved hospitalizations for reasons that were judged by the investigators to be unrelated to treatment. The incidence of treatment-related adverse events was not significantly different among treatment groups (2%, 7-day 1% therapy; 0%. 3-day 1% therapy and 1%, 3-day 2% therapy). One treatment-related adverse event (vaginal burning , 7-day 1% therapy) was judged by the investigator to be severe.

In conclusion, this study demonstrated for patients with mycologically proven vaginal candidiasis, 3-day 2% clotrimazole vaginal cream appears to be safe and shows activity against *Candida albicans* but was not as effective as the 1-day 7% clotrimazole vaginal cream.

Combined Studies

Given in Table 15 are the clinical , mycological and therapeutic cure rates obtained when studies 93-34 and 93-40 are combined as agreed by the sponsor and the Agency in a meting of June 18, 1997. The table also gives the 95% confidence limits on the difference between the 7-day 1% therapy and the 3-day 2% therapy. The 95% confidence limits for clinical, mycological and therapeutic cure rates are within the ± 20% range based on the pooled data from the two studies. Therefore the 3-day 2% is considered statistically equivalent to the 7-day 1% in treating patients with clinically and mycologically proven vulvovaginal candidiasis.

Table 15
Studies 93-34 & 93-40
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	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 (Taro)

Title: A comparative study of a 1-day and a 3-day treatment with clotrimazole vaginal cream 2% (Taro) and a 7-day treatment with clotrimazole vaginal cream 1% (Schering) and a 1-day treatment with clotrimazole vaginal tablet 500 mg [redacted] and a single 150 mg oral dosage of fluconazole [redacted]

Study Objective:

The objective of this study was to compare the clinical efficacy of a 1-day and a 3-day treatment with clotrimazole vaginal cream 2% manufactured by Taro Pharmaceuticals Inc. to a 7-day treatment with clotrimazole vaginal cream 1% manufactured by Schering-Plough Healthcare Products as well a 1-day treatment with clotrimazole vaginal tablet 500 mg manufactured by [redacted] and a 1-day treatment with a single 150 mg oral dosage of fluconazole manufactured by [redacted] (USA) in patients with vulvovaginal candidiasis.

Study Design

The study was conducted at 13 investigational sites in Canada . This study was an investigator blind, parallel group design with patients randomized equally into five treatment groups:

- 1-day oral fluconazole 150 mg tablet [redacted]
- 1-day clotrimazole 500 mg vaginal tablet [redacted]
- 7-day clotrimazole cream, 1% (Schering)
- 3-day clotrimazole cream, 2% Taro
- 1-day clotrimazole cream, 2% Taro

Patients with symptomatic vulvovaginal candidiasis were asked to participate in the study. After obtaining informed consent, the following procedures were performed: a medical history, physical, pelvic and vaginal examinations; a panel of routine clinical laboratory tests; a saline wet mount of a vaginal smear for chlamydia and trichomonads; and a vaginal smear for culture for *Candida species, Neiserria gonorrheae, Gardnerella vaginalis;* and microscopic examination in a 10% KOH wet mount for *Candida* pseudohyphae. Patients of child-bearing potential also had a rapid urine pregnancy test and serum beta RIA test.

Patients with clinical symptoms of vulvovaginal candidiasis who satisfied all other study inclusion and exclusion criteria were enrolled in the study and were given a patient number to which one of 5 treatments was randomly assigned. Patients were randomized in blocks of 10, to treatment with 1-day treatment with a single 150 mg oral dosage of Fluconazole; or a 1-day treatment with clotrimazole vaginal tablet 500 mg; or a 7-day treatment with clotrimazole vaginal cream 1%; or either a 1-day or a 3-day treatment with clotrimazole vaginal cream 2%.

The use of systemic anti-infective, anti-trichomonal, corticosteriod or immuno-suppressive drugs; any local (vulvovaginal) therapy were not permitted at any time during a patient's participation in the study. During treatment, patients were not to use douches, tampons, or contraceptive foams, creams or jellies or any other barrier contraceptive method, and were to abstain from sexual intercourse.

Patients returned to the clinic for follow-up visits at 14-17 days (for visit 2) and 35-42 days (for visit 3) after the start of therapy. Patients were to return their completed diary cards and used or unused packages of medication at visit 2. At each visit, a vaginal examination was performed. clinical signs and symptoms of candidiasis were recorded and specimens of the vaginal secretion were obtained for evaluation by 10% KOH wet mount and by culture for *Candida.* At each follow-up visit, patients were questioned about the occurrence of adverse experiences and the use of any medications since the time of their last visit.

Reviewer's Comment: In a June 18, 1997 meeting between the sponsors and FDA an agreement was reached that the results of the Taro Study (95-50) were to be reanalyzed using the recommended evaluability criteria and statistical methods as used to evaluate the pooled SPHCP studies 93-34 & 93-40. This study compared the safety and efficacy of 5 different formulations in patients with symptomatic VVC. The sponsor has be granted permission by Taro Pharmaceuticals, Inc. for FDA to use the results of this study as the second pivotal study in evaluating the safety and efficacy of the 3-day 2% clotrimazole cream. Therefore only the data that compared the 3-day 2% vaginal cream to the 7-day 1% will be given in the analysis for efficacy. However, safety data from all patients treated with clotrimazole during this study regardless of formulation or strength will be included in the safety analyses.

Demographics

A total of 177 patients was enrolled and randomized to received clotrimazole vaginal cream. Ninety were selected to received clotrimazole 2% for 3 days and 87 were selected to receive clotrimazole 1% for 7 days. There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, weight and height). Patients who received any drug were included in the analyses and their baseline characteristics are listed in Table 16.

Table 16
Clotrimazole Protocol 95-50
Baseline Information, All Patients

	3 DAY 2%	7 DAY 1%
NUMBER OF PATIENTS	90	87
AGE (YRS)		
MEAN	35	35
RANGE	19 - 76	19 - 58
WEIGHT (LBS)		
MEAN	143	140
RANGE	107 - 235	105 - 237
HEIGHT (IN)		
MEAN	63	64
RANGE	57 - 69	57 - 70
RACE		
BLACK	9 (10%)	8 (9%)
OTHER	13 (14%)	15 (17%)
WHITE	68 (76%)	64 (74%)
PRIOR CANDIDIASIS		
NO	31 (34.4%)	23 (26.4%)
YES	59 (65.6%)	64 (73.6%)

Investigators

Thirteen principal investigators from various locations in Canada participated in the study. Their CVs have been reviewed and each is considered well qualified to conduct the study. The names and location of the principal investigators and the number of enrolled and evaluable patients for each treatment group are listed in Table 17.

Table 17
Clotrimazole Protocol 95-50
Therapeutic Cures of Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY ENROLLED	EVALUABLE(%)	CLOTRIMAZOLE 1% 7-DAY ENROLLED	EVALUABLE (%)
Barwin Norman, M. D. Ottawa, Ontario Canada	3	1 (33)	4	1 (25)
Berger, Eduardo, M. D. Ottawa, Ontario Canada	3	2 (67)	4	4(100)
Bilek, William, M. D. Montreal, Quebec Canada	3	0 (0)	2	2 (100)
Climan, Allen B., M. D. Montreal, Quebec Canada	17	14 (82)	16	16 (100)
Guralnick, Mel, M. D. Montreal, Quebec Canada	13	10 (77)	13	11 (85)
Miner, Louise, M. D. Montreal, Quebec Canada	10	10 (100)	9	8 (89)
Morgan, Lionel, M. D. Cornwall, Ontario Canada	2	2 (100)	1	1 (100)
Puranik, Vidya Cornwall, Ontario Canada	0	0 (0)	1	1 (100)
Shatz, Richard, M. D. Montreal, Quebec Canada	0	0 (0)	1	1 (100)
Shinder, Janet, M. D. Montreal, Quebec Canada	9	9 (100)	8	7 (88)
Shore, Mel, M. D. Montreal Quebec Canada	13	10 (77)	12	12 (100)
Wallace, George, M. D. Ottawa, Ontario Canada	2	2 (100)	2	0 (0)
Wiener, Daniel, M. D. Montreal, Quebec Canada	15	14 (93)	14	13 (93)
Total	90	74 (82)	87	77 (89)

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Disposition

The disposition of all patients enrolled in study 95-50 and those eligible for evaluation of efficacy and safety is shown in Table 18. Also, included in the table are the patients excluded from the study with the reasons for exclusion.

Table 18
Clotrimazole Protocol 95-50
Disposition of Patients

	Clotrimazole 3-Day 2%	Clotrimazole 7-Day 1%
Randomized to Treatment	90	87
Treated	77	81
Evaluable for Efficacy	74	77
Non-Evaluable for Efficacy	16	10
Failed Inclusion/Exclusion Criteria	13	6
Protocol Violation	1	2
Lost to Follow-up	2	2
Total Safety Evaluable Population	90	87

The number of evaluable patients that were considered as therapeutic cures are shown in Table 19 by investigator.

Table 19
Clotrimazole Protocol 95-50
Cures of Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	CLOTRIMAZOLE 2% 3-DAY EVALUABLE	CURED (%)	CLOTRIMAZOLE 1% 7-DAY EVALUABLE	CURED (%)
Barwin Norman, M. D. Ottawa, Ontario Canada	1	1 (100)	1	0 (0)
Berger, Eduardo, M. D. Ottawa, Ontario Canada	2	2 (100)	4	2 (50)
Bilek, William, M. D. Montreal, Quebec Canada	0	0 (0)	2	1 (50)
Climan, Allen B., M. D. Montreal, Quebec Canada	14	7 (50)	16	10 (63)
Guralnick, Mel, M. D. Montreal, Quebec Canada	10	7 (70)	11	7 (64)
Miner, Louise, M. D. Montreal, Quebec Canada	10	7 (70)	8	6 (75)
Morgan, Lionel, M. D. Cornwall, Ontario Canada	2	2 (100)	1	1 (100)
Puranik, Vidya Cornwall, Ontario Canada	0	0 (0)	1	0 (0)
Shatz, Richard, M. D. Montreal, Quebec Canada	0	0 (0)	1	0 (0)
Shinder, Janet, M. D. Montreal, Quebec Canada	9	4 (44)	7	1 (14)
Shore, Mel, M. D. Montreal Quebec Canada	10	6 (60)	12	8 (67)
Wallace, George, M. D. Ottawa, Ontario Canada	2	1 (50)	0	0 (0)
Wiener, Daniel, M. D. Montreal, Quebec Canada	14	11 (79)	13	10 (77)
Total	74	48 (65)	77	47(61)

Efficacy

The endpoints analyzed were the clinical , mycological and therapeutic cure rates. The clinical cure rates were 91% for the 3-day 2% clotrimazole cream and 92% for the 7 day 1% clotrimazole cream. The 95% confidence interval limits for the difference in cure rates between the to treatment groups were within 20%. The mycological cure rates for the 3-day 2% cream was 71% compared to a 66% mycological cure rate for the 7-day 1%. The therapeutic cure rates for the 3-day 2% clotrimazole cream was 65% and 61% for the 7-day 1% clotrimazole cream. Table 20.

Table 20
Study 95-50
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	CLOTRIMAZOLE 2% 3-DAY	CLOTRIMAZOLE 1% 7-DAY	2% 3-DAY VS 2% 7-DAY 95% CI
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

Safety

All reported adverse events occurring during the study, whether or not considered to be related to treatment, were tabulated by each treatment group, Table 21. Of the 177 patients that were randomized and received the 3-day 2% clotrimazole or the 7-day 2% clotrimazole cream, a total of 5 patients reported adverse events for a rate of (2.8%). The percent of patients in each treatment group reporting an adverse event is located in Table 21.

Table 21
Clotrimazole Protocol 95-50
Incidence and Severity of Adverse Events

Treatment	Total # Patients	# Patients w/Event	# of Events	Severity— Mild	Moderate	Severe
1% 7 Day	87	3 (3.0 %)	3	1 (33.3%)	1 (33.3%)	1 (33.3%)
2% 3 Day	90	2 (2.0 %)	2	1 (50%)	1 (50%)	0
2% 1 Day	87	2 (2.0 %)	2	1 (50%)	1 (50%)	0
500 mg 1 Day	89	6(7.0%)	6	2 (33.3%)	3 (50%)	1(16.6%)
Diflucan 150 mg	88	2(2.0%)	2	1 (50%)	1 (50%)	0

For patients in the 2% 3-day group the following events were reported:

1. Patient number 225 "had severe pain and burning in vagina with intercourse only" starting 9 days after beginning the Taro 3-day treatment. This event was considered unrelated to study drug.

2. Patient number 747 complained of "mild itch of vulva" 12 days after starting treatment with the Taro 3-day cream. She was treated with hydrocortisone 2% cream. This event is considered possibly related to the study drug.

Three patients who received the 1% 7-day clotrimazole vaginal cream reported the following adverse events:

1. Patient number 205 experienced a heavy period with clots. This patient had a history of heavy periods ("not as severe as this"). This event started 3 days after patient started using the 7-day Schering treatment. She interrupted the study drug until the event was over. There was no recurrence when the drug was restarted. This event is considered not related to study drug.

2. Patient number 504 experienced an axillary rash 2 days after beginning treatment with the 7-day Schering cream. This event is considered remotely related to the study drug.

3. Patient 703 was found to be pregnant 5 weeks after entering the study. Her baseline urine and serum pregnancy tests were negative. She was treated with the 7-day Schering cream, completed treatment and the 3 visits. Approximately 5 weeks later (10 weeks after entering the study) she had a miscarriage. This event is considered unrelated to the study drug.

There were no drug-related adverse events reported by any patient who received the 2% 3-day or the 1% 7-day clotrimazole therapy. The total number of adverse events that were reported as possibly, probably or definitely related to treatment for all treatment regimens is shown in Table 22.

Table 22
Clotrimazole Protocol 95-50
Incidence and Severity of Adverse Events
Possibly, Probably, or Definitely Related to Treatment

Event	Treatment	Total # Patients	# Patients w/Event	# of Events	Severity— Mild	Moderate	Severe
TOTAL	1% 7 Day	87	0	0	0	0	0
	2% 3 Day	90	0	0	0	0	0
	2% 1 Day	87	1 (1.0%)	1	1 (100%)	0	0
	500 mg 1 Day	89	3(3.0%)	3	1(33.3%)	1 (33.3%)	1(33.3%)
	Diflucan 150 mg	88	2 (2.0%)	2	1(50%)	1(50%)	0
PELVIC CRAMPS	2% 1 Day	87	1 (1.0%)	1	1 (100%)	0	0
PRURITUS AND BURNING	500 mg 1 Day	89	1 (1.0%)	1	0	0	(100%)
BLOODY DISCHARGE	500 mg 1 Day	89	1 (1.0%)	1	0	1(100%)	0
RASH & DEPESSION	Diflucan	88	1 (1.0%)	1	0	1 (100%)	0
NAUSEA	Diflucan	88	1 (1.0%)	1	1 (100%)	0	0
SUPPOSITORY FELL OUT	500 mg 1 Day	89	1(1.0%)	1	n/a	n/a	n/a

Summary

The results of the study confirms that the clinical, mycological and therapeutic cure rated obtained from the 3-day 2% clotrimazole vaginal cream is as safe and effective as the 7-day 1% clotrimazole vaginal cream for patients with symptomatic and mycologically confirmed vulvovaginal candidiasis.

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Bridging Study CTZ 97-01

A bridging study was recommended by the FDA at the June 18, 1997 pre-NDA meeting between Taro, SPHCP, the Division of Special Pathogens and Immunologic Drug Products (DSPIDP), and the Division of Over-the-Counter Drug Products (OTC), as a means to demonstrate the therapeutic equivalence of the two formulations used in the NDA clinical studies.

Title: A comparative study of two 3-day treatments with clotrimazole vaginal cream 2% in patients with vulvovaginal candidiasis

Study Objectives:

The primary objective of the study was to compare the clinical efficacy of a 3-day treatment with clotrimazole vaginal cream 2% manufactured by Taro Pharmaceuticals Inc (Taro) to a 3-day treatment with a similar formulated clotrimazole vaginal cream 2%, manufactured by Schering-Plough Healthcare Products Inc. (Schering), in patients with vulvovaginal candidiasis.

Study Design

Patients with symptomatic vulvovaginal candidiasis were enrolled in the double-blind study by eight (8) investigators at various sites in Canada. After obtaining informed consent, the following procedures were performed: a medical history; physical, pelvic and vaginal examination; a panel of routine clinical laboratory tests; a saline wet mount of a vaginal smear for chlamydia and trichomonads; and vaginal smears for culture for *Candida species, N. gonorrheae, G. vaginalis;* and microscopic examination in a 10% KOH wet mount for *Candida* pseudohyphae. Patients of child-bearing potential also had a urine pregnancy test.

Patients with clinical symptoms of vulvovaginal candidiasis who satisfied all other study inclusion and exclusion criteria (see Clinical Studies section, page 6) were enrolled in the study and randomized to receive a 3-day treatment with clotrimazole vaginal cream 2% manufactured by either Schering or Taro. Neither the investigator, the office staff, nor the patient were aware of which treatment was assigned to each patient.

Patients were instructed to take their assigned treatment at bedtime, starting on the day they were enrolled in the study. The use of systemic anti-infective, anti-fungal, anti-trichomonal, corticosteriod or immuno-suppressive drugs; or any local vulvovaginal therapy were not permitted at any time during a patient's participation in the study. During treatment, patients were not to use douches, tampons, or contraceptive foams, creams or jellies or any other barrier contraceptive method, and were to abstain from sexual intercourse.

Patients returned to the clinic for follow-up visit at 3 weeks (21-24 days) after the start of therapy for a repeat culture, history and physical examination. Patients were instructed to return the used or unused package of medication at this visit. Also, a vaginal examination was performed, clinical signs and symptoms of candidiasis were assessed and recorded, and specimens of the vaginal secretions were obtained for evaluation by10% potassium hydroxide wet mount and by culture for *Candida.* At this visit all adverse experiences were recorded. At 5 weeks a telephone interview was conducted to determine whether or not they had experienced a return of symptoms of vulvovaginal candidiasis.

DEMOGRAPHICS

A total of 147 patients was enrolled and randomized to receive clotrimazole vaginal cream 2%. Seventy-four were selected to received clotrimazole 2% (Taro) for 3 days and 73 were selected to receive clotrimazole vaginal cream 2% (Schering) for 3 days. There were no statistically significant differences between treatment groups with respect to demographics and baseline characteristics (age, race, weight and height). Patients who received any drug were included in the analyses and their baseline characteristics are listed in Table 23.

Table 23
Clotrimazole Protocol CTZ 97-01
Baseline Information, All Patients

	3 DAY (TARO) 2%	3 DAY (SCHERING) 2%
NUMBER OF PATIENTS	74	73
AGE (YRS)		
MEAN	36	36
RANGE	21 - 69	20 - 75
WEIGHT (LBS)		
MEAN	144	138
RANGE	110 - 286	92 - 209
HEIGHT (IN)		
MEAN	64	64
RANGE	60 - 71	57 - 69
RACE		
BLACK	6 (8%)	6 (8%)
OTHER	13 (18%)	14 (19%)
PRIOR CANDIDIASIS		
NO	25 (33.8%)	23 (31.5%)
YES	49 (66.2%)	50 (68.5%)

Eight well-qualified principal investigators from various locations in Canada participated in the study. The names and locations of the principal investigators and the number of enrolled and evaluable patients for each treatment group by investigator are listed in Table 24.

Table 24
Clotrimazole Protocol CTZ 97-01
Enrolled and Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	TARO 2% 3-DAY		SCHERING 2% 3-DAY	
	ENROLLED	EVALUABLE (%)	ENROLLED	EVALUABLE (%)
Climan, Allen B., M. D. Montreal, Quebec, Canada	13	11 (85)	13	12 (92)
Guralnick, Mel, M. D. Montreal, Quebec, Canada	14	12 (86)	14	13 (93)
Martin, Markus, M. D. Montreal, Quebec, Canada	3	2 (67)	3	2 (67)
Miner, Louise, M. D. Montreal, Quebec, Canada	5	4 (60)	5	4 (60)
Quiros, Elsa, M. D. Montreal, Quebec, Canada	8	7 (88)	7	6 (86)
Shinder, Janet, M. D. Montreal, Quebec, Canada	6	6 (100)	6	6 (100)
Shore, Mel, M. D. Montreal, Quebec, Canada	7	6 (86)	7	7 (100)
Wiener, Daniel, M. D. Montreal, Quebec, Canada	18	18 (100)	18	18 (100)
Total	74	66 (89)	73	68 (93)

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The disposition of all patients enrolled in Study 97-01 is shown in Table 25. Eight patients in the Taro group and 5 patients in the Schering group were not evaluable for efficacy. All patients enrolled were evaluable for safety.

Table 25
Clotrimazole Protocol CTZ 97-01
Disposition of Patients

	Taro CLT 3-Day 2%	Schering CLT 3-Day 2%
Randomized to Treatment	74	73
Treated	74	73
Evaluable for Efficacy	66	68
Non-Evaluable for Efficacy	8	5
Did not meet eligibility criteria	3	2
Protocol violation after baseline	1	3
Lost to follow-up after baseline	4	0
Total Safety Evaluable Population	74	73

Efficacy Analyses

Patients who satisfied the following criteria were included in the efficacy analyses:

a) Had a 10% KOH wet mount positive for *Candida* pseudohyphae and had a vaginal culture that was positive for *Candida* before the start of therapy.

b) 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 drug was used, the patient was excluded from the efficacy analyses.

c) Completed all visits. A patient who did not return for the follow-up visit because she was declared a treatment failure was included in the analysis as a treatment failure.

The number of patients determined to be therapeutic cures is found in Table 26 listed by investigator.

Table 26
Clotrimazole Protocol CTZ 97-01
Therapeutic Cures of Evaluable Patients by Investigator

PRINCIPAL INVESTIGATORS LOCATION OF STUDY	TARO 2% 3-DAY EVALUABLE	TARO 2% 3-DAY CURED (%)	SCHERING 2% 3-DAY EVALUABLE	SCHERING 2% 3-DAY CURED (%)
Cilliman, Allen B., M. D. Montreal, Quebec, Canada	11	5(45)	12	4(33)
Guralnick, Mel, M. D. Montreal, Quebec, Canada	12	8(67)	13	9 (69)
Martin, Markus, M. D. Montreal, Quebec, Canada	2	2(100)	2	1(50)
Miner, Louise, M. D. Montreal, Quebec, Canada	4	1(25)	4	2(50)
Quiros, Elsa, M. D. Montreal, Quebec, Canada	7	4(57)	6	2(33)
Shinder, Janet, M. D. Montreal, Quebec, Canada	6	3(50)	6	5(83)
Shore, Mel, M. D. Montreal, Quebec,Canada	6	6(100)	7	4(57)
Wiener, Daniel, M. D. Montreal, Quebec, Canada	18	14(78)	18	15(83)
Total	66	43(65)	68	42(62)

There were no significant difference in the clinical, mycological or therapeutic cure rates between the two treatment groups, Table 27. The 95% confidence interval limits for the difference in clinical, mycological and therapeutic cure rates were within ±20%. The clinical cure rates were 77% for the Taro-treated group and 78% for the Schering-treated group.

The mycologic cure rates were 77% for Taro and 75% for Schering. The 3-day Taro treatment and the 3-day Schering treatment confidence intervals were within ±20%.

The therapeutic cure rates demonstrated that the Taro and Schering 3-day treatments with 2% clotrimazole were equivalent (95% confidence limits within ±20%.

Table 27
Study CTZ 97-01
Clinical, Mycological and Therapeutic Cure Rates
Equivalence Analysis Results

	CLOTRIMAZOLE TARO 2% 3-DAY	CLOTRIMAZOLE SCHERING 2% 7-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

Each investigator was instructed to report any clinical event occurring during the study as an adverse event. Out of 147 patients randomized to the two treatment groups, one patient reported an adverse event. Patient 805 who received clotrimazole 2% (Taro) experienced heavy vaginal bleeding after the third dose. This event was reported as remotely related to the study drug. There were no serious drug-related adverse events reported and no patient discontinued the study because of an adverse event.

Summary Study CTZ 97-01

One hundred forty-seven (147) patients were randomly assigned to treatment with one of two different products. Five were excluded due to violations of inclusion/exclusion criteria, 4 patients were loss to follow-up and 4 were discontinued due to protocol violations after enrollment, leaving 134 patients completing the study and evaluable for efficacy (66 Taro and 68 Schering).

The results of this bridging study comparing the therapeutic effectiveness of two formulations of 2% clotrimazole vaginal cream used once daily for three consecutive days demonstrate that the products are equally effective in the treatment of vulvovaginal candidiasis. There were no statistically significant differences between the two formulations in clinical, mycological or therapeutic cure rates.

The safety profiles for the two treatment regimens were not different indicating that the two formulations are equally safe.

Conclusion Study CTZ 97-01

This study demonstrated that the slight differences in formulation between the two clotrimazole 2% vaginal creams manufactured by Taro and Schering respectively had no effect on the therapeutic equivalence of the two products as 3-day once daily intravaginal treatment for patients with symptomatic and mycologically confirmed vaginal candidiasis. The incidence of adverse events was not significantly different between the two treatment groups.

NDA Summary and Conclusions

Efficacy -

At a March 10, 1992 meeting between representatives of the Division of Anti-Infective Drug Product and the Office of OTC Drug Evaluation of the FDA and the Sponsor, Schering-Plough HealthCare Products (SPHCP), agreement was reached on a clinical program for the development of a 3-day clotrimazole therapy for the treatment of vulvovaginal candidiasis. The program consisted of an initial dose ranging study in which three different clotrimazole concentrations would be evaluated, followed by two adequate and well-controlled studies to compare the 3-day therapies identified in the dose ranging study with 7-day 1% clotrimazole vaginal cream therapy which is approved for over-the-counter treatment of self-recognized recurrent vulvovaginal candidasis in the non-pregnant female.

The initial SPHCP clinical program for the development of a 3-day clotrimazole regimen consisted of three studies. The first and second studies (protocols 92-11 and 93-34 compared the 1%, 2% and 4% clotrimazole cream used for 3 days to 1% clotrimazole cream used for 7 days. The third study (protocol 93-40) compared the 3-day 1% and 2% therapies to the 7-day 1% clotrimazole therapy.

Study 92-11 was terminated prematurely because of a high rate of negative vaginal cultures for *Candida* at study entry among patients with positive KOH wet mounts for *Candida* pseudohyphae. Study 93-34 replaced 92-11 and was conducted in two parts. In the first part, the 3-day 1%, 2% and 4% therapies and the 7-day 1% therapy were compared to determine the lowest concentrations of clotrimazole used for 3 days which were at least as effective as the 7-day 1% therapy. In the second part, additional data were obtained on the comparative safety and efficacy of the 7-day therapy and the most effective 3-day therapies identified in the first part of the study. The FDA and Sponsor agreed that Parts 1 and 2 of study 93-34 could be pooled and that this study would serve as one of two adequate and well-controlled studies. After performing an assessment on 96 patients enrolled in Part 1 if the study, it was determined that similar mycological and clinical cure rates were found in all treatment groups and further enrollment of patients in the 3-day 4% group was discontinued. Therefore in Part 2 of study 93-34 only the 7-day 1% and 3-day 1% and 2% therapies were evaluated.

The results of studies 93-34 and 93-40 were submitted by the Sponsor to FDA as NDA 20-574 seeking approval of a 3-day 2% clotrimazole vaginal cream for treating vaginal candidiasis on April 27, 1995. Following a preliminary review of the data submitted with NDA 20-574, the medical reviewer determined that only one of the pivotal clinical trials (93-40) demonstrated equivalence of the 3-day 2% clotrimazole therapy when compared to the 7-day 1% clotrimazole therapy and that two studies demonstrating equivalence were required for approval of the NDA. Based on this review, the Sponsor (SPHCP) withdrew NDA 20-574 on January 29, 1996.

The Sponsor met with DAIDP on April 3, 1996 to further define study requirements for an approvable NDA for its 3-day 2% clotrimazole vaginal cream. At this meeting guidelines for a future 3-day 2% cream study and revised criteria for re-evaluating studies 93-34 and 93-40 and were agreed upon.

Subsequent to this meeting SPHCP became aware of a clinical trial that was being conducted by Taro Pharmaceutical Inc. on a 3-day 2% clotrimazole cream which met the Agency's guidelines. Through a business arrangement with Taro, SPCHP acquired the rights to use the results of this clinical study (95-50) instead of initiating a new study.

On June 18, 1997, SPHCP and Taro held a joint pre-NDA meeting with the Division of Special Pathogen and Immunologic Drug Products (DSPIDP), a newly created Division in ODE-IV responsible for reviewing vaginal antifungals, and the Division of Over-the-Counter Drug Products. The following agreements were reached at that meeting:

- Schering studies (93-34 and 93-40) could be pooled and analyzed according to the revised guidelines of the 4/3/96 meeting and serve as the first of two studies.
- Taro's study (95-50) should be analyzed using the same FDA revised evaluability criteria to be applied to Schering's pooled study and could serve as the second pivotal study.
- The two companies were requested by the FDA to perform a "bridging" study (97-01) that would demonstrate therapeutic equivalence between their respective formulations of the 2% clotrimazole vaginal creams when used for three days.

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 this review.

Given in Table 28 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 28

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**

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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. There was no significant differences between the two formulations in clinical, mycological or therapeutic cure rates.

Table
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 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 in study 95-50 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 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 30 gives the overall incidence of adverse events, regardless of causality.

Table 30
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 31 gives the overall incidence of adverse events that were judged by the investigators to be treatment-related.

Table 31
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 star4t 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 vaginal tablet.

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 statistical 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 the subject of this NDA.

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

A statistical consultation for this NDA was performed by Stella G. Machado, Ph.D., biostatistician of HFD-725. A complete statistical analysis of this NDA may be found in her review October 26, 1998.

[redacted]

Recommendation: The Applicant requests direct OTC approval for the us
Lotrimin-3™Vaginal Cream 2% for 3 days in treating non-pregnant patie
vulvovaginal candidiasis. Based on the results of clinical studies reviewe
recommend approval of this NDA provided the labeling appropriately refl
contained in the OTC labeling review of Cheryl Turner dated September 2

/S/

Joseph K. Winfield, M
Reviewing Medical O

cc: NDA 20-574
HFD-340
HFD-560/OTC
HFD-590
HFD-590/Dep/Dir/RAlbrecht
HFD-590/Team Leader/BLeissa BL 11/4/98
HFD-590/MO/JKWinfield
HFD-590/MO/ECox
HFD-590/PMO/CChi
HFD-725/Stat/SMachado

Concurrence Only
HFD-590/Div/Dir/MG

[redacted]

[redacted]

OTC Div File

Division of Over-the-Counter Drug Products
Medical Officer Review

Applicant:	Schering-Plough Healthcare Products
NDA No:	20-574, Submitted November 25, 1997
Product:	Gyne-Lotrimin 3 Vaginal Cream (clotrimazole 2% - 100 mg)
Date Reviewed:	July 1998
Date Completed:	October 20, 1998

Introduction

Schering Plough is seeking approval of a higher strength clotrimazole 2% vaginal cream (Gyne-Lotrimin 3 Vaginal Cream) for over-the-counter (OTC) use to treat vulvovaginal candidiasis (VVC) in this application. The active ingredient clotrimazole has been approved for vaginal candidiasis since 1976 in the United States, prescription (Rx) and over-the-counter (OTC), in various dosages and formulations. Table 1 provides a summary of clotrimazole formulations that have been approved to date in the U.S. and Canada.

Table 1: List of Clotrimazole Products Approved in the U.S. and Canada

Name	Formulations	Dose	Duration	Status	Approved	Country
GYNE-LOTRIMIN	Vaginal Insert	100 mg	7 day	Rx	1976	U.S.
GYNE-LOTRIMIN	Vaginal Cream	50 mg	7 day	Rx	1978	U.S.
Mycelex-7	Vaginal Insert	100 mg	7 day	Rx	1979	U.S.
Mycelex-7	Vaginal Cream	50 mg	7 day	Rx	1979	U.S.
GYNE-LOTRIMIN	Vaginal Insert	100 mg X2	3 day	Rx	1980	U.S.
Canesten	Vaginal Cream	500 mg	1 day	Rx	1980	Canada
Mycelex-G	Vaginal Tablet	500 mg	1 day	Rx	1985	U.S.
Mycelex Twin Pack	Vaginal Tablet, Ext. Vulvar Cream	500 mg	1 day	Rx	1986	U.S.
Clotrimazole (Taro)	Vaginal Cream	50 mg	7 day	Rx	1988	Canada
Clotrimazole (Taro)	Vaginal Cream	100 mg	3 day	Rx	1988	Canada
GYNE-LOTRIMIN 7	Vaginal Insert	100 mg	7 day	OTC	1990	U.S.
GYNE-LOTRIMIN 7	Vaginal Cream	50 mg	7 day	OTC	1990	U.S.
Mycelex-7	Vaginal Insert	100 mg	7 day	OTC	1991	U.S.
Mycelex-7	Vaginal Cream	50 mg	7 day	OTC	1991	U.S.
GYNE-LOTRIMIN 7 Combo Pack	Vaginal Insert, Ext. Vulvar Cream	100 mg	7 day	OTC	1993	U.S.
Clotrimazole (NMC)	Vaginal Cream	50 mg	7 day	OTC	1993	U.S.
Mycelex Combo Pack	Vaginal Insert, Ext. Vulvar Cream	100 mg	7 day	OTC	1994	U.S.
Clotrimazole (Taro)	Vaginal Cream	50 mg	7 day	OTC	1995	U.S.
Clotrimazole (Taro)	Vaginal Cream	50 mg	7 day	OTC	1995	Canada
Clotrimazole (Taro)	Vaginal Cream	100 mg	3 day	OTC	1995	Canada
Canesten	Vaginal Cream	500 mg	1 day	OTC	1995	Canada
GYNE-LOTRIMIN 3	Vaginal Insert	200 mg	3 day	OTC	1996	U.S.
GYNE-LOTRIMIN 3 Combo Pack	Vaginal Insert, Ext. Vulvar Cream	200 mg	3 day	OTC	1996	U.S.

The clotrimazole 2% vaginal cream has never been marketed in the U.S. This NDA is for direct-to-OTC marketing of this 3-day clotrimazole vaginal cream (Schering Plough product). However, the cream base is the same as the cream base used in the Schering Plough 7-day clotrimazole vaginal cream, which has been marketed since 1978. Taro, Schering's partner in this NDA, has a clotrimazole 2% vaginal cream that has been approved for Rx since 1988, and OTC since 1995 in Canada as a 3-day product. As part of this application Schering Plough has also submitted data from a clinical study (bridging study) to show that the two formulations are similar in adverse event profiles and therapeutic efficacy. Dr. Winfield in HFD-590 will provide the review of this bridging study. Table 2 shows the chemical composition of the Taro and Schering vaginal creams.

Table 2: Formula Comparison of the 1% and 2% Clotrimazole Creams

INGREDIENT [% (w/w)]	Schering Gyne-Lotrimin 7	Schering Gyne-Lotrimin 3	Taro Clotrimazole	Taro Clotrimazole
	1% Cream	2% Cream	2% Cream	1% Cream
Clotrimazole, USP				
Octyldodecanol, NF				
Cetearyl Alcohol				
Cetyl Esters Wax, NF				
Sorbitan Monostearate, NF				
Polysorbate 60, NF				
Benzyl Alcohol, NF				
Purified Water, USP				
Total	100.0000	100.000	100.000	100.000

This review will examine the worldwide post-marketing experience of clotrimazole vaginal cream formulations, including, the clotrimazole 2% vaginal cream (Taro) that is marketed outside of the U.S.

Post-Marketing Experience

I. Clotrimazole 2% Vaginal Cream (Taro's):

Taro's clotrimazole 2% vaginal cream was first approved in 1988 for Rx use in Canada. Since initial marketing in 1989, [redacted] tubes of the Taro clotrimazole 2% vaginal cream have been sold. Taro submitted a listing of all complaints referable to their clotrimazole cream products sold in the U.S. and Canada in the last nine years. Specifically for their clotrimazole 2% vaginal cream, Taro did not receive any adverse event reports.

II. All Clotrimazole Vaginal Cream (Taro's):

During the past 9 years, Taro has sold over [redacted] tubes of clotrimazole vaginal cream products (1% and 2%) in Canada. A total of 22 product complaints were

received by Taro. Four of these reports were determined by Taro to qualify as an adverse event (AE), rather than a product complaint.

Table 3: AEs reported with all Taro's Clotrimazole Vaginal Creams in U.S. and Canada:

#	Place	Date Received	Complaint	Product	Action Taken/Results
#111	U.S.	9/95	Bleaching of skin	Cream 1%	Retention sample assay results all within specs
#190	U.S.	5/97	Burned around lip	Cream 1%	No problem with batch Likely hypersensitivity
#131	U.S.	2/96	Product Ineffective	Cream	Product confirms to all testing
#146	U.S.	6/96	Product did not work	Cream 1%	Returned sample meets specs
#161	U.S.	9/96	Condition not relieved	Cream 1%	Product retained is typical of product

Medical Officer's Comments:

The sponsor did not specifically identify which of the reports were determined by them to be AEs. Upon review of the 22 reports submitted, 5 cases were isolated that could be considered AEs (see Table 3). Three of these reports were for product ineffectiveness, and need not technically be considered AEs. The remaining 2 reports involved adverse effects of the skin. No other information was provided and it remains unclear if these 2 AEs involving the skin were limited to the application site or elsewhere, and if it either were a hypersensitivity reaction. The remainder of the reports was for product complaints such as inclusion of foreign materials, discolouring, loss of labeling, and disruption of packaging. As noted by sponsor, there were no AEs specifically referable to Taro's clotrimazole 2% vaginal cream.

III. All Clotrimazole Vaginal Cream (Schering's):

Schering's clotrimazole 1% vaginal cream has been marketed in the U.S. since 1978. In 1990, the clotrimazole 1% vaginal cream was switched to OTC marketing. An estimated [redacted] of this product has been distributed since its initial introduction. The sponsor noted (in a March 17, 1998 Response to Information Request) that approximately [redacted] of clotrimazole have been sold since 1978. Since that time, a total of 418 non-serious AEs and 2 serious AEs have been reported, which is an "incidence" of [redacted] according to the sponsor. The 2 serious AEs will be described below and the AEs reported for the vaginal cream formulation will be listed in Table 4.

Report #87-10-088: 94 y.o. female with 3-4 month history of urinary tract infections, who experienced lower abdominal pain, proximal anterior lower extremity pain and lethargy during her third to fifth applications of Gyne-Lotrimin Vaginal Cream. Following the fifth application, she was hospitalized with a diagnosis of urosepsis and pyelonephritis. She expired from complications of congestive heart failure and pyelonephritis.

Report #92-12-202 (Portugal): 24 y.o. pregnant woman used Gyne-Lotrimin Vaginal Cream for 4 days as prophylaxis for vaginal yeast infection. She spontaneously aborted during her eleventh week of pregnancy. She was hospitalized, received curettage and antibiotics, and was discharged the next day. Three months earlier , the patient had a spontaneous abortion during her fifth week of pregnancy. Her blood type was RH(-) while her husband's was Rh(+).

Table 4: Number of AEs reported for Clotrimazole 1% Vaginal Cream in the U.S.

Adverse Experience	1997	1996	1995	1994	1993	1992	1991	1990	1989	1988	1987
Therap. Response Decrease			11	27	55	57	42		1	3	
Body as a Whole	2	5	13	5	5	26	1		1	1	
Application Site	1		12	7	9	9	9	1			1
Skin Disorders	4	3	10	5	9			2	1		
Dizziness/Tremor		2	1		1						
Dyspnea			1								
GI Disorders			3			2	3				
Influenza-like Sx						1					
Insomnia	1										
Palpitation						1					
Paresthesia	1					2			2	1	
Parosmia		1									
Purpura			1								
Pyelonephritis											1
Female Reproductive Disorders		5	8	8	6	7	1				
Syncope			1								
Tachycardia	1		1								
Urinary Syst. Disorders						1	1	1			
Death: Fetal					1						

Most of the AEs received in Table 4 were reported by consumers (October 1, 1998 submission in response to a request for additional information). The sponsor stated that the overwhelming majority of cases counted as reproductive system disorders were coded as vaginitis (mainly irritation). Under application site disorders, most of the cases mention burning and some mention pain or irritation. Consumers reported a total of 3 cases as renal and urinary system disorders; 1 case was intercurrent, and 2 were specifically for micturition disorders, which resolved spontaneously.

The sponsor stated that all of the cases reported as a lack of therapeutic response were from consumers, with almost 100% of the consumers seeking a refund. There is minimal information available to verify initial diagnoses, or final outcomes of these reports. The sponsor also stated that the overall frequency of these reports were approximately 1 per [redacted] tubes of cream sold in the first few years of OTC marketing, which declined to approximately 1 per [redacted] tubes of cream sold for the last several years.

Medical Officer's Comments:

The sponsor stated that the serious case of the 94 y.o. woman was reported in 1987 when the product was still marketed as an Rx product. Records from that time were destroyed in a fire and further detailed information about the case is no longer available. The event was considered as being unlikely to be related to the drug. While the 94 y.o. woman's subsequent demise from urosepsis may not be related to the drug, the question remained as to why the drug was used at all. There was no description of symptoms suggestive of vaginal candidiasis in this patient.

In the second serious case, it is reasonable to attribute the fetal loss to Rh incompatibility in a woman with a prior history of spontaneous abortion and Rh incompatibility.

Over the last 10 years, the number of units of clotrimazole 1% vaginal cream sold has remained in the [redacted] with relatively low numbers of AEs reported. As noted by sponsor, the rate of adverse events per [redacted] sold had consistently been <1.

IV. All Clotrimazole Vaginal Cream (Worldwide):

Complete information on the marketing status is not available for all 22 countries, but based on a 1997 report by the World Self-Medication Industry, 12 countries are known to market an OTC clotrimazole vaginal product. Schering-Plough also obtained information on countries where clotrimazole products were marketed from IMS (International Marketing Search). A total of 54 countries worldwide marketed clotrimazole products for vaginal, topical, and/or systemic use. Twenty-three countries were known to market clotrimazole vaginal cream products in strengths of 1%, 2%, and/or 10%. The countries where vaginal clotrimazole cream products are available are listed in Table 5. Countries known to have OTC clotrimazole vaginal products are: Denmark (1996), France, Germany (1994), Ireland (1997), Sweden (1994), United Kingdom (1992), Norway (1995), Australia, Canada, Korea, New Zealand, and USA (1990).

Table 5: Worldwide Availability of Vaginal Clotrimazole Cream Products

Country	1% (50 mg)	2% (100 mg)	10% (500 mg)
Bolivia	X		
Canada	X	X	X
Central America	X	X	
Chile	X		
Columbia	X	X	
Czech Republic		X	
Denmark			X
Dominican Republic	X	X	
Ecuador	X		
France	X		
Germany	X	X	
Italy	X	X	X
Japan	X		
Latvia		X	
Mexico	X	X	X
Pakistan	Concentration Unknown		
Poland	X		
Slovik Republic		X	
South Africa	X		
Spain	X	X	
UK	X	X	X
USA	X		
West Germany	Concentration Unknown		

The sponsor also submitted data from the Collaborating Centre for International Drug Monitoring, World Health Organization, of adverse events (AEs) in the last 10 years. There were a total of 200 AEs recorded from several countries. Table 6 lists some of the AEs reported for which there were >3 reports for that system organ.

Table 6: Number of AEs Reported to WHO (1988 to present):

System Organ	AEs	Number
Application Site Disorders	Application Site Reaction	22
Body as a Whole	Allergic Reaction	8
	Fever	4
	Pain	5
	Dizziness	5
GI System Disorders	Abdominal Pain	4
Reproductive Disorders, Female	Vaginitis	20
Skin and Appendages Disorders	Pruritus	11
	Rash	10
	Rash Erythematous	4
	Urticaria	13
Urinary System Disorders	Face Oedema	4

Medical Officer's Comments:

Overall, the data that is provided on worldwide experience is without sufficient detail for a comprehensive evaluation. There is scant description of the actual adverse events. A breakdown of the adverse events by the specific dosage forms to corroborate that adverse events are not dosage form specific, especially to the cream formulation, would also be useful.

The data from the collaborating Collaborating Centre for International Drug Monitoring cannot be used to make inferences about drug causality. Data is received from different countries with varying methods of data collection and personnel reporting the event. Limited details about each suspected event are received by the Centre, and in most instances, it cannot be proven that the pharmaceutical product or active ingredient caused the event.

Conclusions

There is extensive experience with the use of clotrimazole, both as a topical antifungal agent, and a vaginal antifungal agent. The specific formulation of this 3-day Gyne-Lotrimin vaginal cream (100 mg) under consideration for this NDA has never been marketed in the U.S. The Taro clotrimazole (2%) vaginal cream has been marketed in Canada since 1995, with [redacted] tubes sold since initial marketing in 1989, and no adverse events specifically referable to the product. The clotrimazole 2% vaginal cream has also been known to be marketed in 12 countries, including Canada, worldwide, but no post-marketing data, except for the Taro product in Canada, is available.

Direct information about Gyne-Lotrimin-3 vaginal cream with an increased concentration of clotrimazole from 1% to 2% was provided by the clinical trial experience submitted to this NDA. The full review of the safety data from these clinical trials was undertaken by Dr. Winfield. As reported in the integrated summary (Vol. 2.6), a total of 1416 subjects were included in the integrated safety database. A total of 404 subjects were exposed to the 3-day 2% vaginal cream. The most frequently occurring treatment related AEs were itching, burning, and irritation. Among patients in the 2% vaginal cream group, only 2 experienced treatment-related AEs (vulvovaginal itching and burning), which were reported as severe. The sponsor reported that the overall incidence of AEs was similar across all treatment groups in the various clinical trials. Similarly, there were no differences in treatment-related AEs across all treatment groups in the various trials.

In conclusion, the information from worldwide post-marketing experience of clotrimazole vaginal products does not generate any safety concerns about the use of the clotrimazole 1% vaginal cream, with numbers of AEs reported per [redacted] sold being ≤0.1 from 1987 to 1997. The AEs that were reported with greater frequencies were non-serious and expected, such as application site disorders, skin disorders, and female reproductive disorders. The Taro experience with the 2% cream specifically, over the last 10 years in Canada, provides some measure of comfort that the increased

concentration of the active ingredient did not appear to generate any reports of AEs. The clinical trial data confirmed that the 2% cream is not different from the 1% cream in AE profile. The bridging study demonstrated that the Taro cream is equivalent to the Schering product therapeutically and in safety profiles. Thus, there are no new safety concerns to prevent approval of this product. However, given that this is a direct to OTC formulation, Phase IV postmarketing surveillance requirements must be diligently performed.

/S/

Ling Chi, M.D., M.P.H.
DOTCDP

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Linda M. Katz, M.D., M.P.H.
Deputy Director, 10/26/98
DOTCDP

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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