CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-308

MEDICAL REVIEW

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-308 SUBMISSION DATE: August 31, 2000

Drug Product: Miconazole Nitrate 1200 mg soft gel vaginal insert
Miconazole Nitrate 2% External Cream

Trade Name: Monistat, Dual Pak

Personal Product Company
199 Grandview Road
Skillman, NJ 08558

REVIEWER: Funmilayo O. Ajayi, Ph.D.

TYPE OF SUBMISSION: Prescription to OTC switch

SYNOPSIS: This application is for prescription to Over-The-Counter marketing of miconazole nitrate1200 mg soft gel vaginal insert copakaged with miconazole nitrate 2% external cream. The original NDA for this product was approved in 1998. There is no new biopharmaceutics information in the current application.

RECOMMENDATION: The previously reviewed Biopharmaceutics section of the new drug application for this product (NDA 20-968) is adequate to support the current application for OTC marketing.

Funmilayo O. Ajayi, Ph.D.
Div. of Pharmaceutical Evaluation III

cc: NDA 21-308, HFD-590 (Clinical Division)
HFD-880 (DPE3)

Clinical Review

NDA #:	21-308
Drug name (Generic Name):	Monistat 1 Combination Pack (miconazole nitrate 1200 mg soft gel insert and miconazole nitrate 2% external cream)
Sponsor:	Personal Products Company, previously Ortho (Division of McNeil-PPC)
Pharmacologic Category:	Vaginal antifungal
Proposed Indication:	1-day treatment of vulvovaginal candidiasis for Over-the – Counter (OTC) use
Submission Date:	August 31, 2000
CDER Date:	September 1, 2000

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Executive Summary

I. Recommendations

A. Approval Recommendation

This application is judged to be approvable on the basis of favorable marketing experience with miconazole vaginal products for more than two decades. Tens of millions of patients in many countries, including the US, have been treated for vulvovaginal candidiasis with these products. In the US, the 100 mg, 2% vulvar cream formulation was first approved for prescription use in 1974 and has been available over-the-counter (OTC) since 1991. Other miconazole nitrate formulations approved in the US are 100 mg and 200 mg suppositories, a 200 mg tampon (for prescription use) and a 4% vulvar cream. Worldwide, several formulations and dosages are available in more than 90 countries; one or more of these products is available without prescription in more than 35 countries. No miconazole nitrate formulation has been withdrawn for safety reasons in any country. The 1200 mg ovule is registered in over 20 countries and has been marketed in Denmark since 1982. It is marketed without a prescription in the United Kingdom, Belgium, South Africa, Luxembourg and Canada. In the US, the 1200 mg ovule with 2% external cream was approved for prescription use in June, 1999.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The results of the actual use study were unsatisfactory in regard to the high rate (76%) of *inappropriate* self-selection to use the drug (e.g., failure to have a previous diagnosis of vulvovaginal candidiasis and/or presence of label risk factors such as foul-smelling discharge, abdominal pain, fever, nausea) and the low compliance (10% to 20%) with warnings regarding physician follow-up (i.e., to see a doctor if symptoms do not improve in 3 days or if symptoms do not resolve after 7 days).

The Agency will require that the Sponsor implement a Phase 4 study to demonstrate that consumers will use the product appropriately according to the label. The Sponsor will need to consider label changes and perform another actual use study that shows satisfactory results, especially in regard to the rate of compliance with label warnings. Alternatively, the Sponsor may be able to show with an epidemiological study that OTC use of miconazole nitrate has not resulted in any increase in the rate of complications from pelvic inflammatory disease (PID). Label changes may need to be implemented across the whole class of OTC vaginal antifungals since the low compliance issues are not likely to be unique to this product.

II. Summary of Clinical Findings

The Sponsor wishes to switch the product from prescription to OTC. This application includes the results of an Actual Use Study (Protocol 98-006P). The study was designed to evaluate the safety profile of the combination pack among medically unsupervised

consumers who self-selected to use the study medication for the treatment of vaginal yeast infections. Results of world-wide post-marketing surveillance were also reviewed.

A. Brief Overview of Clinical Program

- MONISTAT® 1 COMBINATION PACK, miconazole nitrate, 1200 mg soft gel vaginal insert and 2% external vulvar cream
- Two pivotal trials (S96-002 and 97-006) for Rx approval of product (NDA 20-968), and one additional actual use trial for present OTC switch application
- Pivotal trials exposed 282 patients to miconazole nitrate, 1200 mg soft gel vaginal insert and 2% external vulvar cream
- The actual use trial enrolled 1413 females (Study 98-006- CR)
- Subjects currently experiencing vaginal yeast infection were recruited
- 1093 subjects exposed in the actual use trial

B. Efficacy

- Demonstration of efficacy in 2 pivotal trials for NDA 20-968 which compared the 1200 mg ovule and 2% cream combination to a previously approved miconazole nitrate formulation (MONISTAT 7 Vaginal Cream—100 mg Miconazole Nitrate).

C. Safety

- Extensive marketing experience world-wide and in the US supports safety of vaginal miconazole nitrate.
- Adverse event rates in the actual use trial were consistent with clinical trials for the prescription product.
- The most common side effects noted in the pivotal trials and the actual use trial include local irritation (burning, itching or discharge), abdominal cramping, and headache. In the actual use trial, reported incidences were: local irritation (burning 9.9%, itching 2.6%), abdominal cramps (2.1%), and headache (4.3%). These were mostly reported by consumers as mild (32%) or moderate (35%) in severity.
- Limitations of the actual use trial include the following: no physician diagnoses or evaluations at entry in the study; follow up at approximately 2 weeks only, and no follow-up on participant contacts with health care professionals unless the participant was hospitalized or saw a study physician.
- Post-marketing surveillance for miconazole since 1996 revealed systemic allergic reactions including several reports of anaphylaxis or shock (including 4 reports from AERS). Possible interactions with anticoagulants have been noted in postmarketing surveillance and the literature.
- Label warnings need to be revised to encompass safety concerns (see Executive Summary, Section I.B.)

D. Dosing

- No issues regarding dose/regimen
- No recommendation for dose modification

E. Special Populations

- Gender differences – not applicable
- Actual use study was performed to characterize OTC use
- No information on ethnic/racial differences in actual use trial. In the original prescription NDA, the applicant examined the distribution of cure rates by age and race and found no significant differences in the distribution of cure rates by age or race. No drug disease interactions were reported during these studies. (NDA 20-968 Monistat 1 Dual Pak, MO review of 6/17/99)
- No pediatric studies available or planned
- Pregnancy use information – Category C

Post-marketing surveillance reveals use by pregnant women. In the actual use study, 23/23 pregnant consumers stated at enrollment that they would use the study drug.

Clinical Review

I. Introduction and Background

A. Drug Identification

Generic name: miconazole nitrate 1200 mg soft gel vaginal insert and miconazole nitrate 2% external cream
Trade name: MONISTAT® 1 Combination Pack
Chemical name: 1-[2,4-Dichloro-p-[(2,4-dichlorobenzyl)oxy] phenethyl] imidazole mononitrate

The study medication consisted of a single dose ovule (miconazole nitrate, 1200 mg) with applicator and a 9 gram tube of 2% miconazole nitrate cream. The ovule is a viscous oil suspension (1200 mg miconazole nitrate in light liquid paraffin, white petrolatum, and lecithin) encapsulated in a soft gelatin shell formulated from glycerin, gelatin and titanium dioxide. The ovule is packaged in a clear plastic and aluminum blister. The 2% miconazole nitrate cream is miscible and white to off-white in color, and it contains benzoic acid, [redacted] isopropyl myrstate, propylene glycol, polysorbate 60, potassium hydroxide, and purified water.

B. Indications

Soft Gel Vaginal Insert: One MONISTAT Soft Gel Vaginal Insert is indicated for the local treatment of vulvovaginal candidiasis (moniliasis).

External Vulvar Cream: External Vulvar Cream is indicated for the relief of external vulvar itching and irritation associated with a yeast infection.

C. Important Milestones in Product Development

- Meeting minutes, 3 March 1999. Sponsor to perform actual use study with full safety update (US and Canada) and label comprehension study
- NDA 20-968 approval letter, 30 June 1999 for miconazole nitrate 1200 mg ovule and 2% cream [MONISTAT 1 DUAL-PAK]

Table 1. Cumulative regulatory approval/decision dates

GYNO-DAKTARIN, ROW89, MICONAZOLE NITRATE 1200 MG VAGINAL CAPSULE

Country	Local Tradename	First Approval	Current Status	First Marketed	Marketing Status
DENMARK	BRENTAN	03-82	=	11-82	=
ITALY	DAKTARIN	10-84	=	04-85	=
NETHERLANDS	GYNO-DAKTARIN	01-85	=	01-85	=
ISRAEL	GYNO-DAKTARIN	02-85	=		DISC 03-91
COLOMBIA	MIRACOL	04-85	=	01-88	DISC
BELGIUM	GYNO-DAKTARIN	11-85	=	02-87	=
UNITED KINGDOM	GYNO-DAKTARIN	01-86	=	07-86	=
G.D.LUXEMBOURG	GYNO-DAKTARIN	06-86	=	04-86	=
KUWAIT	GYNO-DAKTARIN	0"9	=	L	=
IRELAND	GYNO-DAKTARIN	06-89	=	11-89	=
[illegible]	GYNO-DAKTARIN	12-89	=	[illegible]	DISC
BULGARIA	GYNO-DAKTARIN	05-93	=	L	=
SAUDI ARABIA	GYNO-DAKTARIN	06-93	=	12-93	=
ROUMANIA	GYNO-DAKTARIN	08-93	=	L	=
OMAN	GYNO-DAKTARIN	1"5	=	L	=
YEMEN		08-96	=	L	DISC
POLAND	GYNO-DAKTARIN	05-97	=		PLAN
[illegible]	GYNO-DAKTARIN	06-97	=	09-97	=
LATVIA	GYNO-DAKTARIN	01-99	=	L	=
CANADA	MONISTAT	02-99	=	02-99	=
MALTA	GYNO-DAKTARIN	OBT	=	02-87	=
LITHUANIA		OBT	=	L	=
RUSSIA			Exp 12-01		PLAN

First approval: first time the product mentioned in the title was approved in the specified country.
Current approval status: is only given in case date of first approval is not valid anymore. First marketed: first time the product mentioned in the title was marketed in the specified country.
Curient marketing status: is only given in case date of first marketed is not valid anymore.

List of abbreviations :

OBT	Obtained (with date, if available)
EXP	Expected (with date, if available)
WITHD	Withdrawn (with date, if available)
PLAN	Planned (with date, if available)
L	Launched (with date, if available)
DISC	Discontinued (with date, If available)
=	Current status same as first approval/marketed status

[redacted]

The 1200 mg single dose suppository (with or without the 2% vulvar cream) is registered in over 20 countries, beginning with Denmark in 1982 (Table 1). It is currently marketed as a nonprescription product in the United Kingdom, Belgium, South Africa, Luxembourg, and Canada. It is also approved as of June 1999 for prescription use in the

United States. As of July 31, 2000, an estimated 2,688,000 patients worldwide have been treated with the 1200 mg capsule. As of April 30, 2001, the total distribution in the United States of the present formulation, which is a 1200 mg ovule and 2% vulvar cream combination pack, amounted to [redacted] prescription units and [redacted] professional samples. From January 2000 through April 2001, the total distribution in Canada was 128,304 units of the 1200 mg ovules and 174,288 units of the combination pack. The Sponsor states that the product has not been withdrawn in any country due to safety reasons. It has only been withdrawn for commercial/business reasons.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology

Refer to the chemistry review, NDA 20-968. According to the medical review of NDA 20-968, animal reproductive studies of miconazole nitrate preparations in rabbits and rats did not demonstrate effects on pregnancy rate, spermatotoxicity, or teratogenicity. At doses of 80 mg/kg/day in rabbits the number of resorbed fetuses was increased and maternal and fetal toxicity was observed. In rats at the 80 mg/kg/dose, prolonged gestation and an increased number of stillborn pups was noted. Miconazole nitrate has not been found to have mutagenic potential.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

According to the clinical pharmacology/biopharmaceutics review of the prescription NDA 20-968, single dose administration of the 1200 mg ovule resulted in systemic miconazole exposure similar to that observed following recommended dosing with the approved and marketed MONISTAT3 cream (200 mg for 3days). Plasma miconazole levels following intravenous administration have been reported to range from 440 ng/mL up to 6180 ng/mL with no apparent toxic effects. These levels are ~40 to ~580 times the mean C_{max} following single administration of the 1200 mg ovule (10.7 ng/mL). Systemic absorption following administration of a second 1200 mg ovule 48 hours after the first was also studied to gather PK data in the event of improper use. After repeat ovule administration, the mean C_{max} observed is 12.0 ng/mL, still much lower than that after intravenous miconazole. Even with subject 02011, who had elevated miconazole plasma concentrations and C_{max} (28.4 ng/mL after 2nd ovule administration), the levels after IV miconazole would be ~15 to ~200 times greater.

Based on these comparisons, the PK reviewer stated that systemic exposure resulting from single administration of the 1200 mg miconazole ovule is not a safety concern. (Refer to approved NDA 20-968 PK review for additional details.)

B. Drug Interaction

The medical safety update review of NDA 21-261 for the 200 mg, 2% miconazole external cream noted 4 cases of possible or probable interaction with warfarin anticoagulants, leading to increased prothrombin time and/or bleeding.

IV. Description of Clinical Data and Sources

A. Overall Data

Protocol 98-006-P and Report number 98-006-CR: Single blind observational study to evaluate the safety profile of a 1200 mg miconazole 1200 mg vaginal ovule combination pack in the treatment of vaginal yeast infection. Study results are reviewed in Section VII.

Worldwide safety surveillance of miconazole nitrate 1200 mg ovule. Surveillance results are reviewed in Section VIII. The safety information submitted in this application is an update to the information previously submitted in the original prescription NDA 20-968 for this product.

B. Literature Review

For a review of the literature, see NDA 20-968 for prescription miconazole nitrate 1200 mg ovule and 2% cream. The sponsor provided an additional literature reference for the present application, Upmalis DH et al., Single dose miconazole nitrate ovule in the treatment of vulvovaginal candidiasis: two single blind, controlled studies versus miconazole nitrate 100 mg cream for 7 days, *J. Women's Health & Gender-based Medicine,* 9:421-429, 2000 (see Section VII.C).

V. Clinical Review Methods

The actual use study 98-006-CR and the safety update are discussed in this review. There is a separate label review. There was no DSI Audit.

VI. Integrated Review of Efficacy

The efficacy of miconazole nitrate (1200 mg) soft gel vaginal insert and miconazole nitrate 2% cream was established in two pivotal clinical trials by showing equivalence to Monistat 7 Vaginal Cream in the treatment of vulvovaginal candidiasis. The results of these trials can be found in the approved NDA 20-968 for the prescription product.

VII. Integrated Review of Safety

A. Actual Use Study 98-006-CR

Description of trial design

This was an actual use study to evaluate appropriate self-selection and safety of Monistat 1 Combination Pack (1200 mg miconazole nitrate vaginal ovule/2% external cream, 9 g) in the treatment of vaginal yeast infection over a 14-day study period. The study was performed from May through November 1999 at 15 sites in the US. The trial was a multicenter, open enrollment, prospective study in a simulated consumer environment. Data were summarized descriptively. Descriptive statistics were determined for consumers who declined participation and for those who participated in the actual-use portion of the study.

Consumers who decided to use or not use the study medication were described by age, racial/ethnic group, education level, household income, and their reasons for declining study medication use. Based on the medical history information provided, consumers were designated as making appropriate or inappropriate decisions to use study medication. Those consumers who declined and those who decided to use the study medication were evaluated on the "appropriateness" of their decision, based on their "risk factors" which are contraindications according to the label. All consumers who participated in the actual-use portion of the study were tabulated according to their use or misuse of the study medication; adverse events and safety in the use of the study medication; other medical resource use (other vaginal products, and physician, hospital, or ER visits); and their satisfaction with the study medication. The safety profile of the study medication used under medically unsupervised conditions was assessed by evaluating the incidence, type, and severity of treatment-emergent adverse events (TEAE).

> ***M.O. Comment.*** The study procedure did not include follow-up of physician contacts unless the consumer contacted a study physician or was hospitalized.

Objectives

The primary objective of this actual use study was to evaluate the safety profile of the miconazole nitrate combination pack among medically unsupervised consumers who self-selected to use the study medication for the treatment of vaginal yeast infections. The secondary objective was to document patterns of product use in this consumer-simulated environment.

Study Design

This was an all-comers study of female consumers currently experiencing a vaginal yeast infection. Consumers were recruited by advertisement (newspaper, radio, and pharmacy) and by mall intercept. Upon enrollment after completing a screening interview conducted at one of 15 study sites within the US, consumers were provided with free study medication and were reimbursed for continuing participation. They were asked to complete a daily diary and were contacted for a follow-up telephone interview after approximately 14 days.

The protocol called for 1500 consumers to be enrolled at 10 or more sites. A total of 16827 were approached by mall intercept, of whom 15914 were ineligible or unwilling, and 913 consumers were enrolled by participating in the screening interview. In addition, consumers who called a toll-free number were invited to participate. Of 2463 callers, a total of 1395 were eligible to participate, and 1113 made an appointment for a mall interview. The subjects who were recruited by mall intercept were combined for analysis with those who were recruited after calling the toll-free number, for a total of 19,290 inquiries processed. 1413 participated in the enrollment interview, and 1355 enrolled in the actual-use phase of the study.

The study population is summarized in Table 2.

> ***M.O. Comment.*** Dispositions of consumers recruited by mall intercept and by telephone were similar, and these groups are combined in the table. There was a higher proportion of subjects recruited by mall intercept in the actual-use phase [EAUP] group that was lost to follow-up (173/913, or 18.9%), compared to those recruited by telephone (56/500, or 11.2%).

The enrollment phase (EP) included 1413 consumers who participated in the enrollment visit (interview). The eligible use phase (EUP) included 1395 (98.7%) of the consumers who could be evaluated for appropriate choice to use the study medication. A total of 1355 (95.9%) consumers enrolled in the actual-use phase (EAUP) of the study by agreeing to use the study medication, signing informed consent, and taking the study medication home with them. In the EAUP population 1126 consumers had a f/u telephone interview, and 1093 consumers reported using

Table 2. Study Population

Total inquiries by telephone or by mall intercept N = 19290		
Participated in enrollment visit (Enrollment Phase population) N [EP] =1413		
EP eligible for evaluation of appropriate choice to use study medication, N [EUP] = 1395 (98.7% of N[EP])	EP ineligible, did not answer question on use of study medication, N [ineligible] = 18 (1.3% of N[EP])	
Enrolled in actual use phase, took study medication home, N [EAUP] = 1355 (95.9% of N[EP])	Declined to enroll 40 (3% of N[EP])	Would not use study medication 19 (1.3% of N[EP])
Completed follow-up interview N [FU] = 1126 (79.7% of N[EP])	Lost to follow-up 229 (20.3% of N[EP])	
Used study medication N [USM] = 1093 (77.4% of N[EP], 97% of N [FU])	Did not use 33 (2.3% of N[EP])	

the study medication, whereas 229 (16.9%) were lost to f/u. Thirty-three consumers reported not using the study medication.

> ***M.O. Comment.*** The percent lost to follow-up is not unusual for an actual-use study. There is nothing to lead us to believe that these consumers acted differently from those who did participate in follow-up telephone interviews.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- female and at least 12 years old
- access to a telephone and provide a telephone number
- able to speak and read English
- able to provide written informed consent. If under 18 years of age, they had a parent or guardian who also provided written informed consent.

There were no specific exclusion criteria. No concomitant medications were contraindicated in this study.

Demographics

The demographic profiles of consumers in the enrolled (EP) and actual-use (EAUP) populations were similar with respect to median income, race, education level, and age distribution. Among consumers who used study medication, 62.8% were Caucasian, 33.7% were African-American, and 7.6% were Hispanic. The median income was between $30,000 and $39,999. Eighty-four

percent of consumers who participated in the enrollment and actual-use phases of the study were aged between 19 and 59 years, while 10.1% of consumers were aged 60 years or older, and 4.5% were aged 18 years or younger.
The majority (71.4%) of consumers who used the study medication had either completed high school or some college education, and 18.4% indicated they had completed college and/or some postgraduate education. The number of consumers with a low level of education (17) was too small to allow any meaningful evaluation of low literacy on the decision to use in the presence of risk factors.

There were notable differences in the demographic characteristics of the subjects recruited at the various sites. For example, the EAUP subjects from the Fort Lauderdale site were the most affluent (median income $40000 to $49999), the most educated (95.7% high school graduate or above), and the oldest (67% aged 40 years or more). The Houston subjects included the most Hispanics (17.2%) and were more than half African American. Nearly half the Baltimore subjects were African American.

> ***M.O. Comment.*** The study did not provide useful information about usage by low literacy consumers since the number recruited was insufficient. No information was provided as to how the demographics of the study population compare to those for purchasers or users of the product.

Study Procedures

The sponsor employed an agent, [redacted] which was responsible for planning, operational, and analysis of the study, including data management, monitoring, statistical analyses, and medical writing.

The study sites were non-medical offices. The study investigators (one at each site) were female health care professionals qualified to administer medication. The interviewers were trained females. At each site, contact information for a physician sub-investigator was provided at enrollment to consumers for medical consultation. This contact information did not include specific instructions about when to contact a physician. The follow-up telephone interviews were performed by trained female personnel with computer assistance.

Single blinding was accomplished by labeling the study medication as "One Dose Vaginal Yeast Infection Treatment" without identifying the sponsor, the trade name, or miconazole nitrate on the label.

At the enrollment interview, consumers were given a simulation box with a proposed label, instructed to read the label and to choose whether to use the drug. Every subject who chose to use the drug was eligible for inclusion in the actual-use population. Information was then obtained on diagnosis of the current or prior vaginal yeast infections. Informed consent was obtained after the consumer agreed to use the study drug. There was no physician-initiated intervention at any time. Study site personnel did not provide any medical information.

Consumers were provided contact information for the local study physician and instructed to call to report problems or to ask questions according to customary practice during actual use. Study physicians documented reasons for any call and collected medical information pertaining to any

adverse events, follow-up treatments and outcomes. Of the 1,355 consumers in the EAUP group, 13 consumers (1%) made a total of 22 physician contacts.

A toll-free telephone number was established that consumers could call for information. Calls were answered by [redacted] personnel using scripts provided by the sponsor with responses to commonly received questions (e.g., menstrual and sexual concerns, interactions and pregnancy, side effects, accidental ingestion, medical issues and symptom relief, etc.). A total of 50 calls were placed to the toll-free number, pertaining mostly to remuneration and the follow-up interview.

Each consumer was instructed to complete a diary to record the day on which the miconazole nitrate ovule was used and the days on which the cream was used. The diaries also recorded symptom improvement, adverse events, and any concomitant treatments during the 14 day study period.

Per the protocol, a follow-up telephone interview was to be performed between 12 and 19 days after enrollment, to record study drug usage, outcomes of treatment and symptoms, any adverse events and subsequent actions (e.g., medications taken, physician visits). For about 10% of the subjects, the follow-up interview was delayed for up to two months, but these subjects were included in the analysis.

> ***M.O. Comment.*** Long delay in follow-up reduces accuracy of recall and increases uncertainty of results pertaining to dates of use and treatment outcomes, but may provide further opportunity to elicit adverse events.

Protocol violations

One of the health care professionals enrolled herself into the study. One 16 year old consumer lied about her age and enrolled without parental consent. One consumer pretended to read the label but revealed at the follow-up telephone call that she was unable to read. Data from these three consumers were included in the analyses.

Appropriate Self-Selection Rates by Risk Factor

Of 1395 consumers who responded to the question asking if they would use the study medication assuming it were reasonably priced, 1376 stated they would use the study medication, and 19

Table 3. Appropriate choice to use, N =1395 in EUP (vol. 1.3, 11-000037)

Risk factors	Low education level		High education level		All education levels	
	Would use N=17	Would not use N=0	Would use N=1359	Would not use N=19	Would use N=1376	Would not use N=19
No	1 (5.9%)	0	**327 (24.1%)**	8 (42.1%)	**328 (23.8%)**	8 (42.1%)
Yes	16 (94.1%)	0	1032 (75.9%)	**11 (57.9%)**	1048 (76.2%)	**11 (57.9%)**

Number and percent (in parentheses) with appropriate self-selection given in **bold**.

indicated they would not. One thousand fifty-nine (1059, 75.9%) of the 1395 consumers had one or more labeled risk factors (Table 3). Of the 1376 consumers who chose to use the study medication, 1048 (76.2%) had one or more risk factors. On the other hand, among the 19 consumers who chose not to use the study medication, 11 (57.9%) had one or more risk factors.

Table 4. Risk factors and decision to use

DECISION TO USE STUDY MEDICATION ACCORDING TO TYPE OF RISK FACTOR ACROSS ALL GEOGRAPHIC LOCALITIES FOR CONSUMERS IN EUP

	Consumer Decision to Use Study Medication		
Risk Factor Present	Would Use Study Medication (N=1,376) n (%)	Would Not Use Study Medication (N=19) n (%)	Total (N=1,395)
Never had vaginal infection diagnosed by doctor	819 (59.5%)	9 (47.4%)	828 (59.4%)
Unusual baseline symptoms	165 (12.0%)	0 (0.0%)	165 (11.8%)
Frequent vaginal infections	292 (21.2%)	2 (10.5%)	294 (21.1%)
HIV exposure	14 (1.0%)	0 (0.0%)	14 (1.0%)
Currently breastfeeding	2 (0.1%)	0 (0.0%)	2 (0.1%)
Currently pregnant	21 (1.5%)	0 (0.0%)	21 (1.5%)
At least 1 risk factor present	1,048 (76.2%)	11 (57.9%)	1,059 (75.9%)

Those consumers who chose to use the study medication and had at least one of the risk factors are defined as having made an *inappropriate decision to use* the study medication. The most common risk factor (see Table 4) among 1,395 consumers was failure to have a vaginal yeast infection diagnosed by a physician, reported by 828 (59.4%) of consumers. However, 86.4% of this population reported that the current infection was not their first. The second most common risk factor was frequent vaginal infections, reported by 292 consumers (21.1%). The third most common risk factor was any of the following symptoms (see Table 5), abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge, reported by 165 consumers (11.8%).

All of those who had symptoms of abdominal pain, fever, chills, nausea, vomiting, foul-smelling vaginal discharge, or HIV exposure, or who were currently breastfeeding or pregnant, chose to use the drug.

M.O. Comment. The low rates of appropriate self-selection for use of the study drug are not acceptable. Even among consumers with high education level (≥ 9th grade), 75.9% chose inappropriately to use the drug despite one or more risk factors. The number of consumers with low education level (below 9th grade) in this study is too small to permit an assessment of whether appropriate self-selection is affected by education level. The rate of inappropriate decisions to use the product varied by site, with the lowest rate observed in

Baltimore (59.5%). Rates in other sites ranged from 74.8% (Ft. Lauderdale, FL) to 82.1% (Houston, TX).

Table 5. Symptoms present among enrolled consumers (vol. 1.2, 08-000105)

DECISION TO USE STUDY MEDICATION ACCORDING TO SYMPTOMS OF CURRENT VAGINAL YEAST INFECTION AMONG CONSUMERS WHO PARTICIPATED IN THE ENROLLMENT INTERVIEW (EUP)

Characteristics	Consumer Decision to Use Study Medication: Would Use Study Medication (N=1,376)	Would Not Use Study Medication (N=19)	Total (N=1,395)
Consumer with no reported symptoms[a]	8 (0.6%)	2 (10.5%)	10 (0.7%)
Consumers with one or more symptoms of any kind	1,368 (99.4%)	17 (89.5%)	1,385 (99.3%)
Labeled Symptoms Reported			
Burning	492 (35.8%)	4 (21.1%)	496 (35.6%)
Itching	1,087 (79.0%)	12 (63.2%)	1099 (78.8%)
Irritation	363 (26.4%)	5 (26.3%)	368 (26.4%)
Discharge	856 (62.2%)	10 (52.6%)	866 (62.1%)
Total number of consumers with at least one of these symptoms	1,356 (98.5%)	17 (89.5%)	1,373 (98.4%)
Non-VVC Symptoms reported			
Chills	2 (0.1%)	0 (0.0%)	2 (0.1%)
Fever	8 (0.6%)	0 (0.0%)	8 (0.6%)
Odorous discharge	148 (10.8%)	0 (0.0%)	148 (10.6%)
Vomiting	6 (0.4%)	0 (0.0%)	6 (0.4%)
Abdominal Pain	7 (0.5%)	0 (0.0%)	7 (0.5%)
Total number of consumers with at least one of these symptoms	165 (12.0%)	0 (0.0%)	165 (11.8%)
Duration of symptoms			
2 weeks or less	1,133 (82.3%)	11 (57.9%)	1,144 (82.0%)
>2 weeks	188 (13.7%)	4 (21.1%)	192 (13.8%)
Don't know	17 (1.2%)	1 (5.3%)	18 (1.3%)
Other[a]	30 (2.2%)	1 (5.3%)	31 (2.2%)
Symptoms of current infection same as those of previous infection(s)	1,111 (80.7%)	13 (68.4%)	1,124 (80.6%)

[a] Other = verbatim response

a – percent calculations are based on the population of consumers (N=1,376) who would use study medication and participated in the enrollment interview (EUP)

Among the 19 consumers with risk factors who chose not to use the study medication, 9 (47.4%) never had a vaginal infection diagnosed by a physician and 2 (10.5%) had frequent vaginal infections. None of the other risk factors was present among consumers who chose not to use the study medication.

A total of 21 consumers were pregnant at enrollment. All of them chose inappropriately to use the study drug. Two additional consumers became pregnant after enrollment and did not consult a physician.

M.O. Comment. Forty-two consumers answered yes to the question "Are you pregnant?" at the enrollment interview. We cannot explain this discrepancy.

Reported Symptoms and Self Selection

Among the 1376 consumers who indicated they would use the study medication, 1356 (98.5%) reported having at least one of the labeled symptoms of vulvovaginal candidiasis. Seventeen (17, 89.5%) of the 19 consumers who chose not to use the study medication, also reported at least one labeled symptom. The labeled symptoms reported among consumers who chose to use the study medication were itching (79.0%), discharge (62.2%), burning (35.8%), and irritation (26.4%).

One or more symptoms not labeled for vulvovaginal candidiasis (chills, fever, odorous discharge, vomiting, abdominal pain) were reported by 165 (11.8%) of 1395 consumers (see Table 5). All of these 165 consumers chose inappropriately to use the study medication. The most common non-VVC symptom was odorous discharge, reported by 148 (10.8%) consumers. Abdominal pain was reported by 7 (0.5%) consumers, fever by 8 (0.6%) , chills by 2 (0.1%) and vomiting by 6 (0.4%).

M.O. Comment. In keeping with the desire to simulate an OTC environment, there were no physician evaluations to confirm presence of vulvovaginal candidiasis and/or other pelvic infections in enrolled consumers. At least one of the labeled symptoms of vulvovaginal candidiasis was reported by 98.5% of consumers, and it can be presumed that many of the consumers did in fact suffer from this condition. However, a significant proportion of consumers, 11.8%, chose to use the study drug inappropriately despite one or more symptoms of other possible gynecologic infections (chills, fever, odorous discharge, abdominal pain, etc.)

Confirmed Diagnosis and Self Selection

Approximately 40% of the 1,376 consumers who chose to use the study medication had received a current or previous diagnosis of vulvovaginal candidiasis, whereas approximately 60% of consumers had not and chose to use the product inappropriately. Among consumers who chose to use the study medication, ~ 16% had consulted a health care professional for the current infection. Among the 19 consumers who chose not to use the study medication, 5 (26.3%) had consulted a health care professional for the current infection; moreover, 10 of the 19 (52.6%) had been given confirmed diagnoses of vulvovaginal candidiasis, and 9 (47.4%) had not.

M.O. Comment. The proportion of consumers who had a confirmed diagnosis was actually *greater among the subjects who chose not to use the drug .*

Consumer Use Patterns

The follow-up telephone interview was completed by 1126 consumers, all of whom had chosen to use the study medication. Among these consumers 1093 (97.1%) indicated that they used at least one form of the study medication. A total of 881 (78.2%) used both the suppository and the cream, 97 (8.6%) used only the suppository, and 115 (10.2%) used only the cream. Thirty-three (33, 2.9%) consumers did not use either form of the study medication.

Clarity of Instructions
Of the 1126 consumers who completed the telephone follow-up, 1106 (98.2%) reported no problem in understanding the label. Specific sections of the label stated to be unclear were: directions for use of the ovule (12 consumers), directions for use of the cream (2 consumers), "did not know" (1 consumer), and "other verbatim reasons" (5 consumers).

> ***M.O. Comment.*** The present study shows that a significant fraction (19%) of consumers uses only one of the two components of the combination pack. It is noteworthy that nearly all consumers (98.2%) considered the label instructions to be clear. However, previous FDA experience with scenario testing in label studies shows that consumers often answer incorrectly even when they believe instructions to be clear. We cannot be sure from the results of this study whether consumers intentionally do not heed the label or whether there is a problem with label comprehension.

Concomitant Medications
A total of 9.5% of consumers in the EAUP group reported using study drug together with a concomitant prescription or OTC treatment for their yeast infections. Among the 978 consumers who used the suppository, 542 consumers (55.4%) reported no concomitant medication use, whereas 429 (43.9%) reported at least concomitant medication and 4 consumers did not remember.

> ***M.O. Comment.*** While the concomitant medication use was potentially confounding with respect to the safety profile, the AE experience in the actual use trial was consistent with that reported in the pivotal trials and in post-marketing surveillance.

Improvement of Symptoms
Among the 1038 consumers who reported improvement in the symptoms of vaginal yeast infection, approximately 88% reported experiencing improvement within four days of using at least one component of the miconazole nitrate combination pack, and nearly half (48%) reported improvement within 2 days. However, 288 (26.3%) of the 1093 consumers used at least one component of the miconazole nitrate combination pack but did not experience symptom improvement within three days.

The mean number of days between start of treatment with study medication and symptom improvement was 2.8 (±1.7). The percentage of consumers who experienced symptom improvement among those who *used only the cream*, or who *used both* the suppository and the cream, was similar to that for all consumers who used at least one component of the miconazole nitrate combination pack, approximately 95%. Among consumers who used *only the suppository*, the percentage who reported symptom improvement was slightly lower, approximately 89%. The mean number of days elapsed between beginning treatment with the study medication and experiencing symptom improvement was 3.0 (± 1.5) for the consumers who used only the cream, 2.9 (± 1.7) for consumers who used both, and 2.6 (± 1.6) for those who used only the suppository. The percentages of consumers who experienced no symptom improvement in 3 days or less among those who used only the cream or both suppository and cream (25.2% and 26.9%, respectively) were comparable to that of all consumers who used at least one component of the miconazole nitrate pack (26.3%). The percentage was slightly lower (22.7%) for consumers who used only the suppository.

M.O. Comment. These reports of symptom relief are consistent with, but are not sufficient to establish, efficacy of the study drug, in view of the absence of a control arm in the study design. Likewise, the reported differences in symptom improvement among those who used either or both of the study drug components are not clinically significant. Consumers self-selected to use either or both of the drug components. Those who elected to use only one of the components may have had less severe symptoms.

Among the 1093 consumers who used at least one component of the miconazole nitrate combination pack, 979 (89.6%) reported relief in the symptoms of vaginal yeast infection. Approximately 86% experienced improvement in less than 8 days using at least one component of the combination pack, but the remainder (14%) experienced relief in more than 8 days. A total of 242 (22.1%) of the 1093 consumers used at least one component of the combination pack but did not experience symptom relief in less than eight days. Of these 242 consumers, 40 (16.5%) called or visited a health care professional, 57 (23.6%) took other medication, and 2 (0.8%) sought some other (unspecified) form of relief for their symptoms.

M.O. Comment. Treatment of symptoms lasting for more than 7 days without consulting a physician is inappropriate use according to the label. In this study 242 (22.1 %) of the consumers who used the product did not experience relief in less than 8 days. Only 16.5% called or visited a health care professional.

Inappropriate Action With Respect to Unresolved Symptoms

The study label included the warning "if no symptom improvement in 3 days, consult a physician." Of the 259 consumers who did not experience improvement in their symptoms within 3 days, and who used the suppository alone or in combination with the cream, only 26 (10.0%) consulted a physician, whereas 233 (90.0%) did not. The label also warns against using for more than 7 days without consulting a physician. Of a total of 226 consumers who did not experience symptom relief within 7 days, and who used the suppository alone or in combination, only 37 (16.8%) consulted a physician, and 183 (83.2%) did not.

M.O. Comment. This study found low rates of compliance with the label precautions to consult a physician for symptoms that did not improve in 3 days or for symptoms that persisted for more than 7 days.

Consumers Whose Symptoms Continued For More Than 7 Days

The following symptoms were reported by the 226 consumers whose symptoms continued after 7 days: itching was reported by 140 (62%), discharge by 85 (37.6%), irritation by 34 (15%), burning by 33 (14.6%), odor by 9 (4.0%), abdominal pain by 3 (1.3%), rash by 3 (1.3%), nausea by 2 (0.9%), fever by 1 (0.4%) and "other" symptoms reported by 17 (7.5%).

Of the most common symptoms that continued beyond 7 days, the majority were reported either as mild or moderate in severity. However, burning was severe in 5/33 (15.2%) cases, irritation was severe in 4/34 (11.8%) cases, itching was severe in 15/140 (10.7%) cases, and discharge was severe in 4/85 (4.7%) cases. The only other severe symptoms were 2 cases of nausea, 2/3 (66.7%) cases of abdominal pain, and 5/17 (29.4%) cases of other symptoms.

More than half of the 226 consumers indicated that symptoms were "better" after 7 days of therapy. More than 1/3 of consumers reporting burning, irritation, nausea, odor, abdominal pain, or other symptoms indicated their symptoms remained the same. Lingering symptoms worsened for 4/33 (12.1%) of burning, 4/34 (11.8%) cases of irritation, 5/85 (5.9%) cases of discharge, 8/140 (5.7%) cases of itching, 1/9 (11.1%) cases of odor, 1/3 cases (33.3%) of abdominal pain, and 1/17 (5.9%) cases of "other" symptoms.

M.O. Comment. One consumer (number 72007) reported symptoms of severe discharge, itch, nausea, odor, abdominal pain, and stomach cramps. Abdominal pain and itching were worse after seven days, and the consumer saw a physician (not a study physician). This case is suggestive of a pelvic infection that was not treated by the study drug. The line listings included two additional cases (41224 and 111012) of abdominal pain and one additional case of fever (62176) with no other symptom. Consumer 31224 reported severe abdominal pain and moderate itching that were unchanged after use of the medication. Consumer 111012 reported severe burning and itching with moderate lower abdominal pain which was better at 7 days than the pain that existed prior to drug use. The last two consumers did not contact a health professional after 7 days. One participant (012047) who consulted a health care professional for the current infection prior to enrollment was told that she had chlamydia. This participant was not listed among those who used the drug.

These results are difficult to interpret given the study design which did not establish any

Table 6 Adverse Events Reported by Physicians (mod. from vol. 1.2, 08-000129)

Consumer Number	Body System	Preferred Term
041158	Respiratory System	Shortness of Breath; Upper Respiratory Infection
	Special Senses	Dacryops
041270	Genital/Reproductive	Burning, Female Genitalia; Discharge, Female Genitalia; Pruritus, External Female Genitalia
072007	Body as a Whole	Pain, Abdominal; Pyrexia
	Gastrointestinal System	Vomiting
151058	Genital/Reproductive	Discharge, Female Genitalia
092003	Genital/Reproductive	Burning, Female Genitalia; Pruritus, External Female Genitalia
091019	Gastrointestinal System	Gastroenteritis
091056	Cardiovascular	Hemorrhage--vaginal bleeding
091180[a]	Genital/Reproductive	Vaginitis
082945	Body as a Whole	Infection, Fungal
	Genital/Reproductive	Burning, Female Genitalia
049017	Urinary System	Infection, Urinary Tract
151030	Genital/Reproductive	Discharge, Female Genitalia; Irritation, Female Genitalia; Lesion, Female Genitalia
111024 [a]	Genital/Reproductive	Edema, Female Genitalia; Pruritus, Female Genitalia

[a] No follow-up interview performed; events not considered to be treatment emergent adverse events

medical diagnosis for the vast majority of participants. There was no required medical evaluation when symptoms persisted for more than 7 days. There was follow-up of serious adverse events requiring hospitalization, but no follow-up by a study physician if participants consulted their personal physicians. There was no confirmation in most cases that fungal infection was present in the first place or that the drug did or did not eradicate the infection. Likewise, presence of other pelvic infections was not determined.

Safety Evaluation.

The incidence of TEAE (treatment emergent AE) was based on 1093 consumers who reported using the study medication during the follow-up telephone interview. Twelve consumers experienced 25 adverse events which were not self-reported but were reported in physician contact sheets. These events are summarized in Table 6. Two of these events (091180, 111024) were omitted from the set of treatment emergent adverse events because there was no follow-up telephone call.

MO Comment: These 2 patients should have been included by the Sponsor as TEAE, but this correction does not affect the conclusions. One case was a vaginitis and the other was pruritis and edema of the female genitalia (see Table 6).

Five hundred and five TEAEs were reported by 278 (25.4%) of consumers (see Table 7). The body symptoms where the incidence of individual TEAEs were 1% or greater were the genital/reproductive system (15.7%), gastrointestinal system (5.4%), and the nervous system (4.8%). The most common TEAEs within the genital/reproductive system were burning (9.9%), pruritis (2.6%), pain (1.6%), irritation (1.3%), and discharge (1.1%). In the gastrointestinal system, the TEAEs with the highest incidence were gastrointestinal cramps (2.1%) and nausea (1.4%). In the nervous system, the only TEAE with an incidence of $\geq$1% was headache (4.3%). With the exception of pain, these adverse event rates in the genital/reproductive system were slightly lower in the present actual use study than those in the NDA 20-968 clinical trial and historical data. The incidence of TEAEs in the GI system was comparable to those in the NDA 20-968 clinical trial and historical data, while the incidence of headache was lower.

M.O. Comment. The adverse event rates in the actual use study were consistent with those reported for the prescription product (see Table 7).

Emergency Room or Hospital Visits

There were a total of 12 hospital or emergency room visits by study participants (**Table 8**). Two of these were evaluated by the sponsor as serious AEs because they were hospitalized. Both of the serious cases used the cream only, not the ovule. All 12 cases involved one or more of the following symptoms: burning, itching, irritation, pain or discharge. These cases included two spontaneous abortions, one cystitis, another urinary tract infection, one pneumonia, and one varicella.

Table 7. TEAEs and comparison with historical data

Adverse Experience By Body System	Protocol 98-006-P Actual Use Study (N = 1093)		Historical Data (N = 4230)		Protocol 96-002-P				Protocol 97-006-P			
					1200 mg (N = 134)		M7C (N = 123)		1200 mg (N = 138)		M7C (N = 133)	
	No.	%	No.	%	No	%	No.	%	No.	%	No.	%
Body as a whole	22	2.0	332	7.8	9	6.7	11	8.3	4	2.9	12	9.0
Cardiovascular system	18	1.7	50	1.2	2	1.5	2	1.5	4	2.9	3	2.3
Gastrointestinal System	59	5.4	420	9.9	25	18.7	11	8.3	14	10.1	9	6.8
Cramps, GI	23	2.1	128	3.0	8	6.0	3	2.3	5	3.6	3	2.3
Nausea	15	1.4	82	1.9	6	4.5	1	0.8	1	0.7	3	2.3
Genital/Reproductive System	171	15.7	1376	32.5	67	50.0	54	40.9	63	45.7	63	47.4
Burning, female genitalia	108	9.9	710	16.8	32	23.9	29	22.0	39	28.3	34	25.6
Discharge, female genitalia	12	1.1	128	3.0	16	11.9	4	3.0	12	8.7	8	6.0
Irritation, female genitalia	14	1.3	507	12.0	21	15.7	10	7.6	34	24.6	31	23.3
Pain, female genitalia	17	1.6	60	1.4	5	3.7	0	0.0	1	0.7	1	0.8
Pruritus, external female genitalia	28	2.6	582	13.8	30	22.4	35	26.5	22	15.9	36	27.1
Nervous System	52	4.8	682	16.1	35	26.1	36	27.3	19	13.8	18	13.5
Headache	47	4.3	613	14.5	3	23.1	32	24.2	17	12.3	18	13.5
Respiratory System	21	1.9	383	9.1	17	12.7	20	15.2	15	10.9	9	6.8
Skin and Subcutaneous tissue	18	1.7	151	3.6	4	3.0	7	5.3	3	2.2	5	3.8
Urinary System	12	1.1	122	2.9	9	6.7	6	4.5	8	5.8	2	1.5

[1] Historical data summarize all patients valid for safety in all Miconazole Nitrate protocols as of December 1999.

Table 8. ER and Hospital Visits

Participant	Hospitalized	AE Preferred Terms
041042	yes	Trauma/injury Musculoskeletal, NOS ("Hurt My Back"); Irritation, Female Genitalia; Pruritus, External Female Genitalia; Discharge, Female Genitalia
051108	no	Discharge, Female Genitalia; Pain, Abdominal; Pruritus, External Female Genitalia
052043	no	Pain, Female Genitalia; Burning, Female Genitalia; Erythema, Female Genitalia; Pruritus, External Female Genitalia; Discharge, Female Genitalia; Spontaneous Abortion
052064	no	Cystitis; Incontinence, Urinary; Discharge, Female Genitalia; Diarrhea; Pyrexia
062030	no	Pruritus, External Female Genitalia; Discharge, Female Genitalia; Pneumonia
062036	no	Infection, Viral ("Chickenpox"); Pyrexia; Discharge, Female Genitalia; Hypertension
062060	no	Urticaria; Rash, Female Genitalia; Pruritus, External Female Genitalia; Burning, Female Genitalia; Discharge, Female Genitalia
062064	no	Trauma/Injury, Body As A Whole (Car Accident); Pruritus, External Female Genitalia; Discharge, Female Genitalia
062133	no	Ulcer, Skin; Burning, Female Genitalia; Irritation, Female Genitalia
062187	yes	Dry Mucosa, Female Genitalia; GI Disorder, NOS ("Part Of Small Intestine Not Functioning/Stomach Swelling"); Flatulence; Discharge, Female Genitalia
081031	no	Pruritus, External Female Genitalia; Burning, Female Genitalia; Discharge, Female Genitalia; Cough; Upper Respiratory Infection
101040	no	Dizziness; Pain, Gastrointestinal; Menstrual Disorders, NOS; Spontaneous Abortion; Discharge, Female Genitalia; Pruritus, External Female Genitalia; Irritation, Female Genitalia; Infection, Urinary Tract

Adverse Events Reported by Pregnant Consumers

According to the sponsor, 21 consumers indicated that they were pregnant at enrollment. Two additional consumers indicated that they were pregnant during the follow-up interview. Of these 23 consumers, 7 did not have a follow-up interview, and 3 did not use the study medication. A total of 13 pregnant consumers used the study medication. Two of these pregnant users self-reported TEAEs. Consumer 041242 reported mild pyrexia, continued use of the study drug and did not see a physician. Consumer 052043 reported mild abdominal pain and a spontaneous abortion; she did not stop study medication and did not call a physician (but was seen in an ER; **Table 8**). She did not give permission to follow-up with her physician. Another consumer (101040) did not indicate she was pregnant at enrollment or the follow-up interview but reported a spontaneous abortion, stomach pains, unusual period, dizziness and an UTI.

> ***M.O. Comment.*** The label cautions that pregnant women should ask a doctor before use. Of the 21 consumers who were pregnant at enrollment and the 2 additional consumers who were pregnant by the follow-up interview, all elected to participate in the study and use the drug, which is inappropriate according to the label. Seven of these 23 pregnant consumers did not have a follow-up telephone interview and three of them did not use the drug. Of the 13 pregnant consumers who used the drug, none contacted a physician. There is some uncertainty as to the actual number of pregnant participants in the study, as 42 consumers said they were pregnant at enrollment.
> It is not possible to distinguish the 2 spontaneous abortions from the background rate.

Severity of AE

Of the 278 consumers with one or more TEAE who used either the suppository, or the cream, the maximum severity rating was mild for 93 (33.5%), moderate for 90 (32.4%), and severe for 73 (26.3%). These rates are summarized in Table 9.

Table 9. Maximum Severity of Reported Adverse Reactions (from vol. 1.2, 08-000130)

Medication Used	# Consumers Reporting AE	Mild AE	Moderate AE	Severe AE
Cream only	18	6 (33.3%)	6 (33.3%)	3 (16.7%)
Ovule only	35	16 (45.7%)	6 (17.1%)	10 (28.6%)
Both	225	71 (31.6%)	78 (34.7%)	60 (26.7%)

Serious Adverse Events

Two consumers experienced three SAEs which resulted in hospitalization. These occurred in consumers who used only the miconazole cream. This resulted in a point estimate of 0.18% SAEs [95% confidence interval, 0.02% to 0.66%]. Two of the SAEs occurred in one consumer and consisted of abnormal functioning of the small intestine and swelling of the stomach after using only miconazole nitrate 2% external cream, six times over the course of 3 days. Permission to get follow-up information was not given. The second consumer reported a back injury after using only the cream 6 times over the course of 3 days and likewise did not give permission to release further information.

M.O. Comment. None of the reported serious adverse events can be established to have resulted from use of the study drug. The maximum severity of reported adverse events is not significantly correlated to use of cream only, ovule only, or both.

Conclusions

The actual use study of the miconazole nitrate combination pack in a simulated OTC setting found an adverse event rate consistent with that found in the pivotal trials. Of 1093 consumers who used the study drug, there were 2 who reported serious AEs, neither of which was due to the ovule. However, the study protocol did not include physician follow-up of patients with symptoms that did not improve after 3 days or that persisted beyond 7 days, unless they went to a hospital or consulted a study physician, so information on possible pelvic infections may not have been captured.

The study found high rates of inappropriate self-selection to use the drug. Overall, 1048 of the 1395 consumers who reviewed the label (75.1%) decided inappropriately to use the product despite the presence of one or more labeled risk factors. The product was selected for use by 819 of 1395 consumers, although they had never been diagnosed by a physician for vaginal yeast infection. Twelve percent of consumers who chose to use the study medication had one or more symptoms of other possible pelvic infections, namely chills, fever, odorous discharge, vomiting, or abdominal pain. Of consumers whose symptoms did not improve after 3 days of use, 90% failed to consult a physician. Of those who did not have symptom relief after 7 days, 83% continued to use the study drug without consulting a physician. A total of 23 pregnant consumers elected to use the study drug, and none of them consulted a physician.

The study population was predominantly well-educated, with only 1.2% of consumers at low literacy level. The vast majority of consumers (1106/1126, or 98.2%) reported that the label

instructions were clear or did not indicate any problem in understanding the label. It is not clear whether the high rates of inappropriate self-selection or the low rates of compliance with label precautions can be attributed to poor label comprehension. However, one or more actions may be required to ensure that consumers can treat themselves appropriately with OTC antifungals, such as development of an improved label verified by another actual use trial. Also useful may be to conduct an actual use trial in which consumers who elect to use the drug will undergo a medical evaluation with laboratory studies to determine the rate at which they self-treat for the correct condition. Alternatively, it may be possible to show with an epidemiological study that OTC antifungals are not associated with any increase in complications of PID.

B. Worldwide Pharmacovigilance Results

In the US, miconazole nitrate 2% cream was initially approved in 1974 for prescription use as a 14 day treatment for vulvovaginal candidiasis. The vaginal cream was subsequently approved for OTC use in 1991 as a 7 day treatment. Miconazole nitrate vaginal suppositories (200 mg) have been available for prescription use since 1984.

Approved NDAs for miconazole nitrate products include 17-450, 18-520, 18-888, 18-592, 20-670, 20-288 and 20-827. The NDA for the present dosage form was NDA 20-968, which was approved June, 1999 for prescription use (see Table 10).

Table 10. NDA history of miconazole nitrate products

NDA	Approval Rx	Approval OTC	Name	Dosage Form	Dose and Duration of Therapy
17-450	1974		Monistat-7	2% vaginal cream	100 mg qd, 14 days
	1977	1991	Monistat-7	2% vaginal cream	100 mg qd, 7 days
18-520	1982	1991	Monistat-7	100 mg vaginal suppository	100 mg qd, 7 days
18-592	1989		Monistat Tampon 5d	200 mg tampon	200 mg qd, 5 days
18-888	1984		Monistat-3	200 mg vaginal suppository	200 mg qd, 3 days
	1986		Monistat-3 Dual-Pak	200 mg vaginal suppository and external cream	
20-288	1993	1996	Monistat-7 Combin-ation Pack	100 mg vaginal suppository and vulvar cream	100 mg suppository, 7 days
20-670	1996	1996	Monistat-3 Combin-ation Pack	200 mg vaginal suppository and vulvar cream	200 mg suppository, 3 days
20-827		1998	Monistat-3	4% vaginal cream	200 mg qd, 3 days
20-968	1999		Monistat Dual Pak	1200 mg vaginal suppository and 2% vaginal cream	1200 mg suppository and 100 mg qd, 7 days
21-261		2001	Monistat-3 Combin-ation Pack	4% vaginal cream and 2% external cream	200 mg qd, 3 days

The single dose 1200 mg miconazole nitrate vaginal suppository as in this NDA has been approved for marketing over 20 countries, beginning with Denmark in 1982. It is currently marketed as a nonprescription product in the UK, Belgium, South Africa, Luxembourg, and Canada. It is also approved for prescription use in the United States since June, 1999. As of July 31, 2000 an estimated 2,688,000 patients worldwide have been treated with the 1200 mg capsule. As of April 30, 2001 the total distribution in the United States of the present formulation, which is a 1200 mg ovule and 2% vulvar cream combination pack, amounted to [redacted] prescription units and 287,136 professional samples. From January 2000 through April 2001 the total distribution in Canada was [redacted] units of the 1200 mg ovules and [redacted] units of the combination pack.

According to NDA 20-968, the 1200 mg miconazole nitrate ovule for vaginal use has been marketed in the UK under the trade name Gyno-Daktarin™ 1 since July, 1986. Under the trade name Femeron™, the same formulation has been marketed OTC in the UK since July, 1992. In Canada, the 1200 mg miconazole nitrate ovule was approved for OTC marketing in February, 1999 both with and without the 2% vaginal cream.

Table 11. Sales for MONISTAT® 3 in Canada 1995-1997. (NDA20-968, vol. 1.1, 02-000018)

	1995	1996	1997
MONISTAT®3 Ovules	[redacted]		
MONISTAT®3 Dual Pak			
Total MONISTAT® 3			

In NDA 20-968, the sponsor reviewed worldwide safety experience, excluding the United States, from 1981-1989 for all formulations of miconazole nitrate vaginal products. Total sales of these products were [redacted] treatments. The total number of reported suspected adverse events was 165 in 110 patients. There were 17 serious ADEs in 8 patients. Over the same time period, the United Kingdom reported [redacted] treatments sold, with 14 adverse experiences reported. The sponsor estimated that the incidence of adverse experiences is 1 in 160,000, with the incidence of serious ADEs estimated as 1 in 1.5 million. As is commonly found, the incidence of adverse events in post-marketing surveillance is much lower than that found in clinical trials. The distribution of the adverse events reported in postmarketing surveillance is similar to that found in clinical trials.

Two adverse reactions after using the 1200 mg ovule were reported to the UK Department of Health Medicines Control Agency over the period January 1992 to February 1998: one was diarrhea and headache, and the other was dizziness and headache.

In 1994, the 400 mg for 3 day formulation was approved for over-the-counter sale in Canada (note that the MONISTAT® 3 preparation in Canada is the 400 mg ovule, as opposed to the 200 mg suppository approved in 1996 for OTC marketing in the United States). The Canadian 3-day product delivers a total dose of 1200 mg of miconazole nitrate, which is the same total dose as

the 1200 mg miconazole nitrate vaginal ovule (although the latter is delivered as a single dose). Sales data are presented in Table 11.

Since the launch of OTC MONISTAT®, adverse experiences have been collected by [redacted] in Canada utilizing an 800 telephone number, as is done in the U.S. AE's are reported from the time of launch to the end of 1997 in Table 12. This table breaks out local irritation from other adverse experiences. Review of these data indicate a low rate of adverse experiences for MONISTAT® 3 products in Canada, but a rate that is well above the average of 1 in 160,000 reported by the sponsor in NDA 20-968.

Table 12. Adverse Experiences MONISTAT 3 – Canada (mod. NDA20-968, vol. 1.1, 02-000018)

Formulation	1994		1995		1996		1997		Total
	Irritation	Other	Irritation	Other	Irritation	Other	Irritation	Other	
MONISTAT® 3 OVULES	7	0	50	4	54	3	37	1	156
MONISTAT® 3 COMBINATION PACK	8	0	66	1	105	6	98	2	286
ANNUAL TOTALS	**15**		**121**		**168**		**138**		**442**

M.O. Comment. The average adverse event rate for MONISTAT 3 (both forms) was 24 per 100,000 units sold from the incidences reported for the years 1995 through 1997. The vast majority of these reports involved local irritation.

Table 13. Sales in Canada 1998-2000. (vol. 1.2, 08-000146)

Product	Sales (units)			Product	Sales (units)			Product	Sales (units)		
	1998*	1999	2000		1998*	1999	2000		1998	1999**	2000
MONISTAT 7 Cream				MONISTAT 3 Ovules				MONISTAT 1 Ovule			
MONISTAT 7 Suppositories				MONISTAT 3 Combination Pack				MONISTAT 1 Combination Pack			
MONISTAT 7 Combination Pack											
Total MONISTAT				Total MONISTAT 3				Total MONISTAT 1			
Grand Total MONISTAT				Grand Total MONISTAT 3				Grand Total MONISTAT 1			

*8/98-12/98. **Launched 2/99

Canadian Safety Update: 1998-2000

The 1200 mg ovule formulation has been marketed OTC in Canada since February, 1999, both with and without the 2% external cream. Canadian sales data are summarized for this miconazole formulation, for the 7-day, 200 mg suppositories (Monistat 7), and for the 3-day, 400 mg ovules

Table 14. Adverse Events, Canadian Monistat OTC Products. (vol. 1.2, 08-000147)

	Monistat 1 2/99-7/00	Monistat 3 8/98-7/00	Monistat 7 8/98-7/00	Monistat Dermal Cream 1/99-9/99	Monistat NOS 8/98-7/00	TOTAL ADVERSE EVENTS
Hypersensitivity NOS		1		1		2
Headache NOS		1	1			2
Neurological Symptoms NOS	1	1	1			3
Abdominal Pain NOS		4	3			7
Gastrointestinal Disorder NOS	1	3				4
Nausea		3				3
Genital Pruritus Female	8	23	10			41
Rash Generalised	1	8	4	1		14
Skin Disorder NOS		1	2			3
Erythema NEC			1			1
Back Pain		2	3		1	6
Abortion Spontaneous NOS			1			1
Vaginal Discharge		1	1			2
Vaginal Haemorrhage		1	1			2
Genital Disorder Female NOS	3	3	1	1		8
Vulval Oedema	2	9	4			15
Vulvovaginal Discomfort NOS	29	171	78	1	14	293
Drug Ineffective		1				1
Nonspecific Reaction	2	5	3			10
Pyrexia		2	1			3
Total Adverse Events	47	240	115	4	15	**421**
Total Contacts	**36**	**194**	**92**	**3**	**15**	**363**

(Monistat 3) in Table 13. Canadian OTC labeling for Monistat products is very similar to that for OTC Monistat products in the US.

The sponsor collected Canadian adverse event reports using a toll-free 800- telephone number. The numbers of adverse events and their distributions by body system are listed in Table 14.

M.O. Comment. The average adverse event rate for all Canadian MONISTAT forms combined was 29 per 100,000 units sold from the total distribution of 1,251,023 and the 363 total adverse event contacts reported over the period covered in Table 13 and Table 14. This rate is nearly equal to that for Monistat 3 during 1994-1997 as shown in Table 12. It is noted that the AE contact rate for Monistat 1 (1200 mg ovules) during 1999-2000 was 13 per 100,000 from the 36 AE contacts per [redacted] this rate is lower than for the average of all Monistat formulations.

The vast majority of reported AEs in Table 14 were vulvovaginal discomfort and general pruritus. Other adverse events of note were hypersensitivity reactions and generalized rash (16/421, 3.8%), headache or other nonspecified neurological symptoms (5/421, 1.2%), abdominal pain (7/421, 1.7%), fever (3/431, 0.7%), back pain (6/421, 1.4%), nausea or nonspecified GI disorder (7/421, 1.7%). There was one report of spontaneous abortion and two additional reports of vaginal hemorrhage. There was only one lack-of-effect report. The US adverse events experience in Table 7 is generally similar.

[redacted] **Safety Update: 8/16/91--8/15/96**

A report was released from the [redacted] providing a 5-year safety update for the gynecological formulations of miconazole nitrate, covering the period August, 1991- August, 1996. This report summarizes safety data assessed by the pharmaco-vigilance staff of [redacted] All AEs reported directly to the Company,

compiled from the scientific literature, or forwarded by national regulatory authorities are analyzed and entered into the international AE database. All events reported in association with miconazole, without reference to presumed causal relationship to the drug, constitute the starting point for this safety update. Those events assessed as having causality of possible or higher by both the reporter and by [redacted] staff are included in the safety update report. The causality ratings were (lowest to highest): doubtful, possible, probable, and very likely.

Based on the safety data assessed, an International Product Information Document (**IPID**) is updated periodically. Previous IPID revisions were made in June 1994 and April 1996 dealing with the interaction of the miconazole nitrate formulations with latex. The current (1996) listing is that "Contact should be avoided between certain latex products such as contraceptive diaphragms or condoms and Gyno Daktarin since the rubber might be damaged". Two new listed side effects were added following the August 1996 report, dealing with allergic reactions and abdominal/pelvic cramping associated with drug administration. These points are included in the current U.S. labeling.

It is estimated that, over the time period August, 1991 to August, 1996, approximately [redacted] women were treated with miconazole nitrate-containing products (sales figures do not include U.S. over-the-counter sales). Of the [redacted] women treated, about [redacted] used the 1200 mg ovules. A total of 1454 adverse experiences were assessed, including U.S. OTC reports, with 822 cases meeting the CIOMS-II international reporting criteria for periodic drug safety update summaries. *These AE reports are not classified by dosage.* More than 95% of the cases (1,409 of the 1,454 cases received and 797 of the 822 that met the reporting criteria) are consumer reports and are poorly documented, especially with respect to concomitant drugs and diseases.

> ***M.O. Comment.*** While AE reports were received from 6 countries (Belgium, Denmark, Germany, Netherlands, Sweden, USA), the vast majority of the reports (1432/1454) originated from the US. Nearly all of the reports resulted from use of the 2% vaginal cream or the vaginal suppository formulations (100 mg and 200 mg) marketed in the US.
>
> According to the sponsor, an average of [redacted] packages of the 2% cream or the 100 mg suppository were sold annually from 1991 to the present. Vaginal burning and itching were the most frequently reported side effects, followed by hives/skin rash, and lower abdominal pain/cramps. However, the incidence of all of these events declined after 1991. There were 823 reports of vaginal burning/itching among consumers using these products in 1991 and only 337 similar reports in 1996 on sales of [redacted] units, respectively (rates of 8.2 and 3.4 per 100,000 respectively). This suggests that under-reporting of AEs with miconazole nitrate may have increased with time as the product became more familiar.

The [redacted] report cited 704 reports of application site reaction, 26 of application site edema and 2 of contact dermatitis. In addition, there were 181 reports suggestive of a *systemic* allergic reaction, including two serious cases (#22944 and #30157). Also noted was that a total of 81 patients reported abdominal/pelvic cramping. Some related events were also received: abdominal discomfort (n=2), abdominal pain (n=17), abdominal pain lower (n=7). The nature of these events is unknown and they may be related to the indication rather than the drug. The IPID has been revised to list both allergic reactions and abdominal cramping.

Three adverse experiences were reported related to pregnancy. One report (#10100) involved a woman who conceived the day after finishing a course of vaginal cream and whose daughter had multiple birth defects and died after 10 months. Insufficient documentation was provided to assess this report. There were two reports of spontaneous abortion: in one case (#6810) the miscarriage occurred 5 weeks into pregnancy after use of a single miconazole nitrate suppository; and in the other (#34515) miscarriage was reported after use of three suppositories but the reporter considered the case to be suspicious.

M.O. Comment. The [redacted] 1991-1996 safety update is supportive of the safety of miconazole nitrate, but the reports came predominantly from the US, where the 1200 mg ovule was not marketed.

Table 15.[redacted] Safety Report 1996-1999 (vol. 1.2, 08-000148)

Source Classification					
Body System	**Reaction**	**Health Authority**	**Literature**	**Spontaneous**	**Total**
Application Site Disorders	Application Site Reaction			5	5
Body as a Whole	Allergic Reaction			1	1
General Disorders	Anaphylactic Reaction	1	-	-	1
	Drug Interaction	1	2	-	3
	Efficacy, Lack of	-	-	1	1
	Fever	-	-	1	1
	Pain	-	-	1	1
Centr & Periph Nervous System Disorders	Burning Mucosal	-	-	2	2
	Burning Skin	-	-	1	1
	Headache	-	-	2	2
	Vertigo	-	-	1	1
Foetal Disorders	Abortion	-	-	1	1
Gastro-intestinal Disorders	Abdominal Pain	-		1	1
	Nausea	-		1	1
Platelet, Bleeding & Clotting Disorders	Bruise	1		-	1
	Gingival Bleeding			-	1
	Hemorrhage NOS			1	1
	Nosebleed			-	1
	Prothrombin Time Prolonged	1	2	1	4
	Purpura	-	-	1	1
Psychiatric Disorders	Sleeplessness	-	-	1	1
Reproductive Disorders, Female	Burning Feeling Vagina	-	-	1	1
	Vulvovaginitis	-	-	1	1
Skin and Appendages Disorders	Pruritus Vulvae	-	-	1	1
	Urticaria	-	-	1	1
	Vaginal Itching	-	-	2	2
Total # Patients		2	2	16	20

- = no reports. Medically confirmed and causality of possible, probable or very likely (highest rating)

[redacted] **Safety Update: 8/16/96–8/14/99**

In October, 1996, the statement of adverse reactions was revised to read "*Most frequently reported were local irritation, pruritis and burning sensation, especially at the start of the treatment. Complaints of pelvic cramping, hives, skin rash have also been reported.*" It is estimated that during this interval, approximately 36.9 million women were treated with miconazole nitrate vaginal cream, 14.6 million were treated with miconazole nitrate vaginal ovules and 15.7 million were treated with miconazole nitrate capsules.

During the period covered by this periodic safety report a total of 80 initial reports were received. In 78 cases, the report states that attribution estimate was at least "possible" and only these cases were discussed in the report. Two of these cases were derived from the literature, 2 from a health authority, and 16 were spontaneous. Table 15 lists the distribution of adverse event reports included in the [redacted] database (medically confirmed with causality evaluated as possible, probable, or very likely, the last being the highest possible causality rating).

M.O. Comment. During this period a total of 58 spontaneous reports were received that were evaluated as "medically unconfirmed" and excluded from the safety update. Most of these cases originated from Canada and most involved local irritation. There was *only one report from the US* in this total. There were a total of 20 additional reports from health care professionals which were included in the [redacted] safety update, *none of which originated from the US.*

The [redacted] report listed 2 serious adverse events, an anaphylactic reaction and a spontaneous abortion. In addition a case of purpura was described:

--Report [redacted] described a serious anaphylactic reaction leading to hospitalization. The patient was a 33-year old woman with a history of atopy, asthma and unspecified allergy who developed itching and generalized rash within a few hours of the miconazole suppository application. She subsequently developed a swollen throat and breathing difficulties. She was hospitalized and recovered within 24 hours with epinephrine, corticosteroid and antihistamine treatment.

--Report [redacted] involved a 28-year old pregnant patient who used the vaginal cream once at 12 weeks. She was prescribed bromopride (if necessary) and folate in her first trimester. She used miconazole vaginal cream once at 12 weeks of pregnancy. After the first application, there was "extravasation of vaginal secretion". She complained of a stomach ache and was switched from folic acid to vitamins, minerals, calcium gluconate and calcium lactobromic by her physician. Three days later, the patient experienced abdominal pain, hemorrhage, and a spontaneous abortion. A week later she also experienced headache and sleepiness.

--Report [redacted] involved purpura in a 73-year old diabetic woman treated with miconazole and itraconazole for vaginitis. Other medications were metformin, glibenclamide, furosamide, coloxyl, pethidine, as VesparaxTM (nystatin, triamcinolone, neomycin, ganicidine). Biopsy results reported showed a leucocytoclastic vasculitis. The reaction abated after discontinuation of miconazole and itraconazole.

There were 4 cases of a possible drug interaction with warfarin anticoagulants (refer to safety review for NDA 21-261). A warning has been added to the labeling for vaginal miconazole products stating that a doctor or pharmacist should be consulted if the

consumer is taking a prescription blood-thinning medicine such as warfarin, because bleeding or bruising may occur.

Safety Update: 8/15/99–8/14/00

The exposure of women during the reporting period was estimated as approximately treatment courses, including courses of the 1200 mg ovule and 2% cream combination pack. During this period a total of 221 spontaneous reports was received, of which 1 was reported in the literature, 4 others were rated as medically confirmed, and 215 were medically unconfirmed spontaneous reports. The overall incidence of spontaneous reports was 0.67 per 100,000 treatment courses. The cumulative number of serious unlisted events worldwide from 15 August 1971 to 14 August 2000 was 18, including one death.

M.O. Comment. One of the serious cases occurred in the present 8/15/99-8/14/00 reporting period, the spontaneous abortion report JRFBEL1999000736 (involving a Canadian consumer who used the external cream while 2 months pregnant and who was taken to an ER with abdominal cramping and pain; spontaneous abortion occurred). The other serious cases are presumed to have occurred prior to this reporting period and would have been discussed in previous safety updates if evaluated as possible, probable, or very likely in causality.

The following two cases were discussed in the safety update, neither one serious:

--JRFBEL2000000161 USA was a report of probable interaction with warfarin in a 53 year old woman. She had been on a 3 day miconazole vaginal capsule treatment when she noticed ecchymosis and a prolonged prothrombin time was measured. Warfarin was held for 2 days. Shortly after she again used miconazole vaginal capsules and her warfarin dose was reduced prophylactically and the INR remained within therapeutic range. One year later miconazole was again given and the warfarin dose was reduced prophylactically. Her INR value rose above her normal range and warfarin had to be held for 2 days.

--JRFUSA2000000168 was a report of paresthesia in a 77 year old female treated with cisapride for intestinal motility problems and with concomitant drugs including miconzaole, paracetamol, rofecoxib and temazepam. She had a history of mastectomy, involuntary movements of the hands, arms and head, allergy to various drugs and a seizure following lidocaine use. Concomitant disease was reported as tremor. The adverse events reported were paraesthesia, pruritus, diplopia, cataract, vision abnormal, personality disorder, hallucination, dyskinesia, nausea, abdominal pain, fall and injury attributed only nausea to use of miconazole.

The following 10 cases, all Canadian, were consistent with systemic allergic reactions, and none were classified as serious: JRFBEL1999001837 involved an anaphylactoid reaction after using 400 mg ovule, including drop in BP, difficulty swallowing, swollen eyelids; JRFBEL1999001638 desquamative erythema after using 400 mg ovule; JRFBEL2000000182 non-application site bullous eruption after using 400 mg ovule; JRFBEL2000000259 non-application site bullous eruption after using 1200 mg ovule; JRFBEL2000000131 non-application site bullous eruption and skin exfoliation after using 400 mg ovule; JRFBEL1999000947 hives after using 400 mg; JRFBEL1999000367 facial erythematous rash after using 2% cream; JRFBEL1999001397 facial rash with skin flaking after using 400 mg ovule; JRFBEL1999001865 facial rash morning after 1200 mg ovule; JRFBEL1999002047 rash on torso after using 2% cream. Two of these ten cases involved the 1200 mg ovule.

Because of the drug interaction report (JRFBEL2000000161), Personal Products Company will perform an absorption study in patients with vaginitis.

M.O. Comment. In summary, the [redacted] safety update reports support the safety of miconazole nitrate. Continuing reports of application site reactions, mainly burning irritation, itching, abdominal pain and cramping warrant mentions in product labeling. In addition, warnings about allergic reactions and about potential interaction with warfarin anticoagulants are justified.

[redacted] Safety Update: Usage in Pregnancy

As of the 14 August 2000 safety update, the [redacted] cumulative pregnancy database included a total of 35 cases, of whom 22/35 took miconazole by a vaginal route. Ten of these 22 cases were reported *prospectively*, of which there were 6 healthy outcomes, one induced abortion, one spontaneous abortion, and 2 abnormal outcomes with congenital abnormalities:

-- female of unknown age conceived one day after completing 7-day course of miconazole cream; female infant had multiple unspecified congenital defects, died at 10 months (JPDA#694 JIPSY #PRIUS10100)

-- female of unknown age used miconazole cream during first trimester and delivered male infant with two inguinal hernias, one very large testicle and small penis (JPDA#698 JIPSY #ORTUS1969).

The remaining 12 of 22 cases were reported *retrospectively* and included two healthy outcomes, two induced abortions, five spontaneous abortions (including JRFBEL1999000736 mentioned above), and 3 abnormal outcomes in uninterrupted pregnancies (one congenital abnormality, one neonatal abnormality, and one stillbirth):

-- female of unknown age, HIV positive, treated with didanosine 400 mg/d during second trimester of pregnancy, lamivudin 300 mg/d and calcium folinate 15 mg 3 times/week during the third trimester of pregnancy; zidovudine 500 mg/d used during second and third trimesters. Used miconazole and econazole ovules for 6 days in third trimester. Female infant at birth had right cervico-subclavicular arteriovenous fistula. An operation was planned at the age of 6 months. (JPDA #23630 JIPSY #JAFRA40672)

--female 31 years old used nystatin suppository and miconazole vaginal cream during pregnancy. Also took vitamins and minerals. Male infant had persistent fetal circulation that probably needed surgery (JPDA #691 JIPSY #ORTUS2510)

--female 35 years old used miconazole ovule at 40 weeks into pregnancy, entered labor the next day. Stillbirth, female, born macerated weighing 2 lbs, where time of fetal death could not be determined. (JPDA #27300 JIPSY #JRFBEL1999001903)

M.O. Comment. Continued surveillance is needed to determine if the rates of birth defects and spontaneous abortions with miconazole use in pregnancy are above background. The label warning should be continued against use in pregnancy or breast-feeding unless so advised by a physician. According to the medical review of NDA 20-968, animal reproductive studies of miconazole nitrate preparations in rats and rabbits did not demonstrate effects on pregnancy rate, spermatotoxicity, or teratogenicity. At doses of 80 mg/kg/day in rabbits the number of resorbed fetuses was increased and maternal and fetal toxicity was observed. In rats at the 80 mg/kg/dose, prolonged gestation and an increased

number of stillborn pups was noted. Miconazole nitrate has not been found to have mutagenic potential.

Table 16. AERS reports to May, 2001 for 1200 mg combination product

Adverse Event	Total
Vaginal burning or irritation	14
Vaginal discharge	1
Vulvovaginal discomfort and abdominal cramping	1
Drug ineffective	1
Abdominal cramping	1
Tachycardia (NOS) for 20 minutes following use	1
Total adverse events	**19**

AERS reports

As of May, 2001 the US spontaneous reporting system since the 1999 approval date contains 23 reports under the trade name or verbatim name Monistat Dual Pak and related names. A total of 19 of these reports were specifically for Monistat Dual Pak (the present product), none of which was serious (see Table 16). Through April 2001, the total distribution in the United States of the 1200 mg ovule and 2% vulvar cream combination pack was [redacted] prescription units and [redacted] professional samples.

M.O. Comment. The rate of spontaneous reports in the US is similar to that in Canada and is higher than that in the rest of the world. The 19 AERS reports yield an incidence rate of reports between 6 and 17 per 100,000 units (assuming that all or none of the professional samples were distributed, respectively).

AERS was also searched for all reports of miconazole deaths. Three reports involved miconazole nitrate by vaginal route and consisted of 1 stillbirth and 2 congenital anomalies.
There were 5 reports with a topical indication that were likely unrelated to use of miconazole nitrate:

- One HIV male patient on multiple medications who died of sepsis
- One male patient on two additional medications (diflucan, Bactrim) who died of hemorrhage
- Study report of three elderly men who used miconazole/zinc preparations for diaper dermatitis

There were 7 reports with an unknown (not reported) route:

- One spontaneous abortion, drug given for yeast vaginitis, likely a vaginal route
- A 46 year old female treated for necrotizing pancreatitis with miconazole and other drugs, route not specified
- A 1 year old male treated for trichosporon infection with miconazole and other drugs, route not specified
- A 64 year old male treated for pulmonary mycosis with miconazole and other drugs, route not specified
- A 36 year old male on zyprexa and miconazole for rash (likely topical)

- A 38 year old male with HIV, treated with multiple drugs including miconazole (formulation unknown), developed Stevens-Johnson syndrome, encephalopathy
- An adult male who received daktarin and anticoagulants, no additional information provided

Of these cases with unknown indication, only the spontaneous abortion and the male who received daktarin anticoagulants are possibly linked to the use of miconazole. Moreover, the spontaneous abortion, the stillbirth, and the two cases of lethal congenital abnormalities did not involve use of the 1200 mg ovule.

WHO database

Data from the World Health Organization (WHO) database includes adverse events associated

Table 17. WHO database for miconazole, 1998 (vol. 1.2, 08-000149)

Body System/Adverse Event	Number of Reports
Application site disorders	
application site reaction	92
Body as a whole - general disorders	
allergic reaction	17
anaphylactoid reaction	11
fever	13
edema	16
pain	25
therapeutic response increase	13
Central & peripheral nervous system disorders	
Headache	15
Paresthesia	19
Gastrointestinal system disorders	
abdominal pain	20
nausea	20
vomiting	17
Platelet, bleeding and clotting disorders	
coagulation time increased	17
prothrombin decrease	18
purpura	10
Reproductive disorders, female	
vaginal hemorrhage	18
vaginitis	141
vulva disorder	35
Skin appendages disorders	
dermatitis contact	35
eczema	13
pruritus	85
rash	81
rash erythematous	30
rash maculo-papular	27
urticaria	42
Urinary system disorders	
hematuria	12

Summarized from October 1998 report.

Adverse events included herein are from all miconazole formulations including topical/vaginal, oral and IV

with the use of all forms of miconazole, including vaginal, topical, oral and intravenous. Table 17 lists any event reported 10 or more times in the October 1998 report. A single patient can report more than one event. The distribution of adverse events is similar to what has been seen in other post-marketing databases.

It is cautioned that the information is not homogenous with respect to sources of information or the likelihood that the drug caused the reported reaction. Adverse event reports are transmitted by National Centers, some of which accept reports only from medical practitioners or from a wider spectrum of health workers. Some include reports from pharmaceutical companies and some do not. Some accept reports from consumers. Some National Centers assess the likelihood that the drug caused the reaction, and some do not. The frequency of reporting can be influenced by publicity and/or the nature of the reaction. No information is provided on the number of patients exposed to the drug.

The sponsor provided an updated summary (see Table 18) of the WHO database as of December, 2000, with adverse event reports through 21 November 2000. The number of reports increased substantially over the previous period, probably because of prior under-reporting to WHO. The updated WHO database summary is broken down by route of administration, and highlights are given in Table 18 for adverse events from vaginal products only (chosen on the basis of large numbers or special interest). Entries in bold are for totals for organ system classifications, while the indented subentries are specific event classifications included in the organ systems totals, but which do not necessarily add up to the organ system total. For example, there were 88 application site disorders reported, which included 85 application site reactions.

M.O. Comment. The distribution of adverse events is broadly consistent with that reported in other databases. Most of the reports originated in the US. The vast majority of adverse events involved vulvovaginal discomfort, which presumably includes any or all of pruritis, burning, irritation, pain, or discharge. This classification term is nonspecific and does not correspond to US terminology. Some allergic reactions were captured in the 'Body as a Whole' organ system classification, but additional cases may have been coded elsewhere. Under 'Cardiovascular disorders, general' (not shown in Table 18) are found one report of shock and one report of hypotension. Under 'Skin and appendages' there are 2 reports of erythema multiforme, plus one report each of erythema nodosum, Stevens-Johnson syndrome, dermatitis exfoliative, eczema, bullous eruption, and fixed eruption. Under 'Urinary system disorders' there is one report of facial edema and one report of eyelid edema. Under 'Respiratory system disorders' there are 4 reports of dyspnea, 1 of asthma, and 1 of throat tightness.

The reports under 'Platelet, bleeding, and clotting disorders' included 3 reports of bleeding NOS, 1 hematoma, and 1 thrombocytopenia. Any interaction with anticoagulants would presumably be captured here, so this problem is rarely reported.

The reports under 'Urinary system disorders' included one hematuria and one cystitis, plus three reports of dysuria, two of increased frequency, and two of urethral disorder NOS.

The four deaths were all reported from the US. No specific information is available on these cases from WHO. A search of AERS reports specifically involving the 1200 mg ovule did not reveal any serious cases. Another search of AERS for all miconazole nitrate deaths found four reports associated with vaginal use, consisting of one stillbirth, one spontaneous abortion, and two cases of congenital abnormalities (see AERS reports).

Table 18. WHO database for miconazole vaginal route, 2000

Body System/Adverse Event	Number of Reports
Application site disorders	**88**
application site reaction	85
Body as a whole - general disorders	**988**
allergic reaction	7
anaphylactic shock, anaphylactoid reaction	4
back pain	40
death	4
edema, edema genital, vulval edema	178
fever, pyrexia	16
pelvic pain	42
therapeutic response decreased	637
Central & peripheral nervous system disorders	**147**
headache	52
burning	44
paresthesia	8
Fetal disorders	**9**
abortion	5
congenital anomalies, malformations	4
Gastrointestinal system disorders	**360**
abdominal pain	241
cheilitis	23
nausea	38
Platelet, bleeding and clotting disorders	**5**
Reproductive disorders, female	**3892**
vaginal discharge	572
vaginal hemorrhage	123
vaginal pain	201
vulvovaginal discomfort	2709
vaginitis, vulvovaginitis	184
Skin and appendages disorders	**1150**
dermatitis	145
erythema	13
pruritus	100
pruritis genital	557
rash erythematous	22
rash genital	44
rash	105
skin irritation	42
urticaria	65
Urinary system disorders	**22**

Summarized from cumulative reports through 21 November 2000.
Adverse events included herein are from vaginal miconazole formulations only

There was one report of unintended pregnancy in the WHO database. It is not known whether the latter involved use of a latex contraceptive device.

B. Literature

The integrated review of safety in NDA 20-968 was supplemented by one literature report. Upmalis DH et al. J Women's Health & Gender-Based Medicine 9, 421 (2000). This article is the published report on the pivotal trials in the approved NDA 20-968 for miconazole nitrate 1200 mg ovule and 2% cream [MONISTAT 1 DUAL-PAK].

These trials were randomized, single-blind, multi-center, controlled clinical studies (96-002 and 97-006) of patients with documented vulvovaginal candidiasis. The studies were designed to determine the efficacy and safety of miconazole nitrate 1200 mg ovule, administered in one dose, in combination with miconazole nitrate 2% cream applied 'as needed' for relief of itching and burning. A two-arm study design was used, with an active control consisting of Monistat 7 (miconazole nitrate 2% cream, seven doses at 100 mg per dose for a total of 700 mg). Monistat 7 is currently available OTC. The studies were single-blinded by dispensing of drug in standard white cartons but were open thereafter. Patients were randomized in equal numbers to either the ovule plus cream treatment or the Monistat 7 treatment. These studies found the two treatments to be equivalent in terms of efficacy and safety. Study 96-002 enrolled a total of 278 patients, and study 97-006 enrolled 280 patients.

C. Summarize Critical Safety Findings and Limitations of Data

The actual use study 98-006-CR was supportive of the safety of miconazole nitrate 1200 mg ovule and 2% cream in OTC use with caveats in regard to appropriate self-selection. There were no serious adverse events found to be attributable to the ovule. Principal limitations of the study were lack of medical evaluations and limited duration and information on follow-up. Worldwide marketing surveillance shows that this miconazole nitrate formulation has a satisfactory safety record, subject to the usual limitations of under-reporting in pharmacovigilance and incomplete information for comprehensive evaluation.

VIII. Dosing, Regimen, and Administration Issues

There are no issues with the recommended dose. The actual use study revealed low rates of consumer compliance with label directions (see Section VII. A).

IX. Use in Special Populations

- Gender differences – not applicable
- Actual use study was performed to characterize OTC use
- No information on ethnic/racial differences in actual use trial. In the original prescription NDA, the applicant found no significant differences in the distribution of cure rates by age or race. No drug disease interactions were reported during these studies. (From MO review of NDA 20-968)

- No pediatric studies available or planned or requested for this indication.
- Pregnancy use information – Category C—the label contains a warning against use in pregnancy unless advised to do so by a health care professional

X. Conclusions and Recommendations

A. Conclusions

Primarily safety information was requested for the present OTC switch application. Results of an actual use study and world-wide post-marketing surveillance reports were reviewed. These results were supportive of safety in OTC use with caveats in regard to *appropriate self-selection* and data quality, namely, the lack of medical evaluations and limited duration of follow-up during the actual use study and the non-uniformity of under-reporting in post-marketing surveillance from country to country.

B. Recommendations

This application is judged to be approvable provided the Sponsor makes a commitment to a Phase 4 study to demonstrate that consumers will use the product appropriately according to the label. The Sponsor will need to make label changes and perform another actual use study that shows satisfactory results, especially in regard to the rate of compliance with labeled warnings. Alternatively, the Sponsor may be able to show with an epidemiological study that OTC use of miconazole nitrate has not resulted in any increase in the rate of complications from pelvic inflammatory disease (PID). Label changes may need to be implemented across the whole class of OTC vaginal antifungals since the low compliance issues are not likely to be unique to this product.

The results of the actual use study were unsatisfactory in regard to the high rate of inappropriate self-selection to use the drug (e.g., failure to have previous diagnosis of vulvovaginal candidiasis, presence of label risk factors) and the low compliance with label warnings (e.g., to see a doctor if symptoms do not improve in 3 days or if symptoms do not resolve after 7 days). However, there is vast worldwide experience with the active ingredient both for prescription as well as OTC products, and there were no serious adverse events in the use study found to be attributable to the 1200 mg ovule.

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