CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020968

CHEMISTRY REVIEW(S)

JUN 11 1999

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-968 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/11/99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	6/30/98	6/30/98
Amendment	8/11/98	? (sites)
Amendment (BC)	9/30/98	10/1/98
Amendment (BC)	10/8/98	10/9/98
Amendment (BC)	3/1/99	3/2/99
Amendment (BZ)	3/16/99	3/17/99
Amendment (BB)	3/30/99	3/31/99
Amendment (BC)	5/4/99	5/4/99
Amendment (BL)	5/7/99	5/10/99
Amendment (NC)	5/18/99	5/19/99
Amendment (NC)	6/2/99	6/3/99
Amendment (NC)	6/7/99	6/8/99
Amendment (NC)	6/11/99	?

NAME & ADDRESS OF APPLICANT:

Advanced Care Products
P.O. Box 6024
691 U.S. Route 1 South
North Brunswick, New Jersey 08902
Ph# (732) 524-1675

CONTACT:

Diane Herron, Director, Regulatory Affairs

DRUG PRODUCT NAME:

Proprietary: Monistat 1 Dual-Pak (proposed but under discussion)
Established: Miconazole Nitrate, USP
Code #: n/a

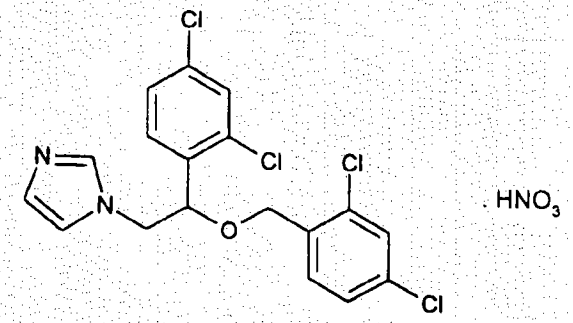
PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of vulvovaginal candidiasis.

DOSAGE FORM: Vaginal Insert and External Cream

STRENGTHS: 1200 mg insert and 2% cream
ROUTE OF ADMINISTRATION: Intravaginal and external vulvar

Rx/OTC: Rx
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Miconazole nitrate, $C_{18}H_{14}Cl_4N_2O.HNO_3$, MW = 479.15
(1) 1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate
(2) 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole mononitrate
CAS 22832-87-7



SUPPORTING DOCUMENTS:

DMF [redacted] DMF [redacted] DMF [redacted]

RELATED DOCUMENTS:

N/A

[redacted]
APPEARS THIS WAY ON ORIGINAL

CONSULTS:

Trademark review (complete 5/25/99, satisfactory).
Site inspection (complete 3/15/99, satisfactory for all seven sites).
Microbiology consult (complete 1/21/99, satisfactory).
Environmental Assessment (categorical exclusion request acceptable).

REMARKS/COMMENTS:

This NDA submitted by Advanced Care Products (ACP), provides for a dual pack containing miconazole nitrate soft gel vaginal insert (1200 mg) and miconazole nitrate external cream, 2%, as a one dose treatment for vulvovaginal candidiasis. Monistat External Vulvar Cream, 2%, is an approved and marketed product (NDA 17-450) with a [redacted] which was approved via SCF-043 in 1997 with the expiration date of 36 months. Monistat External Vulvar Cream in packaged in the [redacted] Therefore, the current application contains the CMC information only for the other, [redacted] The trade name proposed by the applicant in the original application for this new product as Monistat 1 Dual-Pak, was unacceptable. As a result of the consult with the Nomenclature and Labeling Committee, the applicant established a new trade name for this product, Monistat Dual-Pak, which is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Monistat Dual-Pak (miconazole nitrate vaginal insert and miconazole nitrate vaginal cream). The related GMP and product specific inspections of the manufacturing facilities have been completed and found satisfactory. From the chemistry, manufacturing and controls viewpoint, the NDA is recommended for approval.

/S/ [redacted]
Dorota Matecka, Ph.D.
Review Chemist, HFD-590

/S/ [redacted] 6/11/99
Norman R. Schmuff, Ph.D.
Team Leader, HFD-590

cc: Org. NDA 20-968
HFD-590/Division File
HFD-590/Team Leader/NSchmuff
HFD-830/DivDir/CChen
HFD-590/Chem/DMatecka
HFD-590/MO/ECox
HFD-590/CSO/CChi
District Office

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020968

PHARMACOLOGY REVIEW(S)

 JUN 2 8 1999

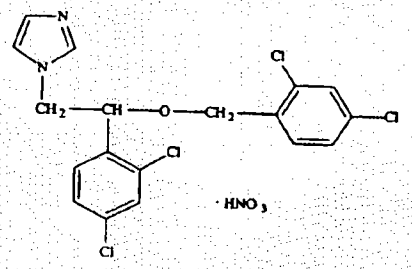
Division: HFD-590
Division of Special Pathogen and Immunologic Drug Products

Drug Product: MONISTAT® 1 DUAL-PAK

MONISTAT® (miconazole nitrate vaginal insert) Soft Gel Vaginal Insert, 1200 mg and
MONISTAT® (miconazole nitrate cream) External Vulvar Cream, 2%

Sponsor: Advanced Care Products Personal Products Company
199 Grandview Rd.
Skillman, NJ 08558-9418

Drug substance miconazole nitrate
Molecular weight 479.15
Chemical formula $C_{18}H_{14}Cl_4N_2O.HNO_3$
Chemical name 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl) oxy]phenethyl]-imidazole mononitrate.



Formulations

MONISTAT® (miconazole nitrate vaginal insert) Soft Gel Vaginal Insert, 1200 mg [redacted] miconazole nitrate [redacted] liquid paraffin [redacted] white petrolatum, [redacted] lecithin [redacted]

MONISTAT® (miconazole nitrate cream) External Vulvar Cream, 2% contains miconazole nitrate USP, 2%, purified water, USP, [redacted] propylene glycol, [redacted] stearyl alcohol, [redacted] cetyl alcohol, [redacted] polysorbate 60, [redacted] isopropyl myristate, [redacted] benzoic acid, [redacted] potassium hydroxide, [redacted]

Manufacturers

(soft gel capsules) [redacted]

(miconazole cream) [redacted]

(miconazole nitrate) [redacted]

Related NDA's IND's and DMF's

IND [redacted]
NDA 17-450 MONISTAT 7 Vaginal cream
NDA 18-040 MONISTAT injectable (i.v) (withdrawn)
NDA 18-520 MONISTAT 7 Suppositories
NDA 18-592 MONISTAT 5 Tampons
NDA 18-888 MONISTAT 3 Suppositories
NDA 20-288 MONISTAT 7 Combination Pack
NDA 20-670 MONISTAT 3 Combination Pack
NDA 20-827 MONISTAT 3 Vaginal Cream
DMF [redacted]
DMF
DMF
DMF
DMF

Introduction

Miconazole nitrate is a synthetic imidazole antifungal agent, which exerts its antifungal activity by the inhibition of the ergosterol biosynthesis in the cell membrane of the pathogenic organism. Miconazole also affects the synthesis of triglycerides and fatty acids and inhibits oxidative and peroxidative enzymes. Miconazole nitrate cream is

locally active when administered intravaginally and vaginal concentrations of miconazole nitrate remain above the normal range of MIC's for 48 hours after treatment. The amount of drug entering the bloodstream is low and once therapy is complete, miconazole nitrate is cleared quickly from the blood.

Monistat vaginal cream (100 mg) was approved in the US in 1974 as a 14-day therapy and as a 7-day therapy in 1977. Monistat 7 vaginal suppositories (100 mg) have been available since 1982 and Monistat 3 vaginal suppositories (200 mg) have been available since 1984. Monistat 3 vaginal cream (200 mg) was approved in 1998. In addition to the above US approvals, other approval of miconazole nitrate outside of the US include a 400 mg vaginal [redacted] which was approved in Canada and a 1200 mg [redacted] which is used in 34 countries.

Most of the toxicology studies of miconazole nitrate have been reviewed in previous NDA's (listed on the previous page). The remaining studies are reviewed below.

Toxicology Studies Review

1. **Acute oral toxicity of miconazole nitrate (1200 mg) vaginal [redacted] in rats. [redacted] March 1998.** [redacted] **Report [redacted] 1325**

This study was designed to determine the effects of oral administration of miconazole nitrate in the form of the bulk [redacted] mass used in the manufacture of miconazole nitrate (1200 mg) vaginal [redacted].

A single dose of [redacted] (2300 mg/kg miconazole nitrate) was administered orally to 10 Sprague Dawley rats (five animals per sex per dose group). Records were kept of mortality, clinical signs and toxic effects twice daily for 14 days. Body weight was recorded before dosing and at the end of the study.

All rats appeared normal throughout the study. There were no significant effects seen in body weight or at necropsy.

The minimal lethal dose of miconazole nitrate (as bulk [redacted] was greater than 2300 mg/kg in rats. This is equivalent to a human dose of greater than 384 mg/kg based on body surface area comparisons.

2. **Acute dermal toxicity of miconazole nitrate (1200 mg) vaginal [redacted] in rabbits. [redacted]-1324. March 1998.**

This study was designed to determine the acute dermal toxicity potential of miconazole nitrate (1200 mg) vaginal [redacted] following a single dermal application to rabbits.

Ten rabbits were shaved with electric clippers 24 hours before application of a single dose of the test material (the [redacted] used in the manufacture of the vaginal [redacted] which contains 920 mg/kg miconazole nitrate). A sleeve of plastic sheeting was fitted over the shaved trunk and secured. Records were kept of bodyweight change, mortality, necropsy findings and signs of toxicity 1, 2.5 and 4 hours after dosing and then twice daily for a total of 14 days.

All animals appeared normal from study day 1 to the end of the observation period. There were no gross changes observed in any of the animals at terminal necropsy.

The acute dermal minimum lethal dose is greater than 920 mg/kg (equivalent to a human dose of greater than 294 mg/kg).

3. **Primary Eye irritation study of miconazole nitrate (1200 mg) vaginal [redacted] in rabbits. [redacted] 1323. March 1998**

This study was designed to determine the ocular irritation potential of miconazole nitrate (1200 mg) vaginal [redacted] in rabbits.

The bulk ointment (0.1 ml) was instilled directly into the right eye of three rabbits and remained unrinsed. The remaining three rabbits were treated with the test article and then irrigated with 20 ml lukewarm tap water for about 4 seconds after each instillation The left eye was used as the untreated control. Observations for ocular irritation were made approximately 24, 48 and 72 hours after treatment.

Minor conjunctival irritation was observed at the 24-hour time point in 1 of the three animals with unrinsed eyes. The irritation had disappeared by the 48-hour observation point. The maximum mean irritation score in unrinsed eyes was 0.7 of a possible maximum score of 110. There was no irritation in rinsed eyes.

4. **Primary skin irritation study of miconazole nitrate vaginal [redacted] in rabbits. D [redacted] 1322. March 1998.**

This study was designed to determine the irritation potential of miconazole nitrate (1200 mg) vaginal [redacted] when administered to abraded skin of rabbits.

An 8x8 cm area was shaved from the left and right flanks of 6 rabbits using an electric clipper. The right dorsal side of each animal was abraded with a 22-gauge hypodermic needle just before application of 0.5 ml of test article. Test article was applied to each intact and abraded site. The test article was then covered with gauze and the entire trunk wrapped with plastic wrap. After a 24-hour exposure period, the covering material was removed and the excess test article was wiped from the area. Observations for dermal irritation were made 24 and 72 hours after patch removal.

No erythema or edema was observed at the 24 hour or 72 hour time point. The mean dermal irritation score was 0 (non-irritating).

Other studies

Studies using a higher concentration of miconazole (4%) showed that it was a slight irritant to rabbit skin, abraded or non-abraded. It was not however irritating to the penile mucosa. One study also showed that miconazole nitrate 4% did not exhibit the potential to produce delayed hypersensitivity in the skin of guinea pigs.

Summary and conclusions

Miconazole nitrate has been approved for use in numerous products in the United States since 1974. MONISTAT® DUAL-PAK, which consists of MONISTAT® (miconazole nitrate vaginal insert) Soft Gel Vaginal Insert, 1200 mg and MONISTAT® (miconazole nitrate cream) External Vulvar Cream, 2% contains drug products which have been tested in humans and animals. No findings in any of the preclinical or clinical studies would preclude the approval of this drug product.

/S/ [redacted]

Owen G.McMaster, PhD
Pharmacology/Toxicology Reviewer,
Division of Special Pathogen and Immunologic Drug Products.

Concurrences:
HFD-590/Ralbrecht /S/ 6/28/99
HFD-590/KHastings /S/ 6/28/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020968

STATISTICAL REVIEW(S)

APR 15 1999

Statistical Review and Evaluation

NDA #:	20-968
Applicant:	Advanced Care Products
Name of Drug:	MONISTAT® 1 DUAL-PAK® (miconazole nitrate 1200 mg soft gel insert and miconazole nitrate 2% external vulvar cream)
Documents Reviewed:	NDA Index and Summary sections (Vol. 1.1) and the Statistical section (Vols. 1.12-1.21) dated June 30, 1998, and diskettes containing SAS datasets provided by the sponsor.
Type of Report:	Statistical Review
Indication:	Treatment of vaginal yeast infections (candidiasis)
Medical Reviewer:	Dr. Edward Cox (HFD-590)

I. Introduction

Miconazole nitrate has been available in several vaginal formulations for the treatment of vulvovaginal candidiasis for 20 years. The currently marketed MONISTAT® Vaginal Cream (miconazole nitrate 2%) delivers 100 mg of miconazole nitrate daily for seven days. Three day treatment is available with MONISTAT® 3 Vaginal Suppositories which contain 200 mg of miconazole nitrate per suppository and MONISTAT® 3 Vaginal Cream (miconazole nitrate 4%) which delivers 200mg of miconazole nitrate per dose. This application is for a miconazole nitrate (1200 mg) vaginal [redacted] for the single dose treatment of vulvovaginal candidiasis. The purpose of the clinical program for miconazole nitrate (1200 mg) vaginal [redacted] was to demonstrate therapeutic equivalence to a reference standard seven day therapy in the treatment of patients suffering from vulvovaginal candidiasis.

Two pivotal Phase III studies were conducted (96-002 and 97-006). Both studies, identical in design, were randomized, controlled, parallel group, comparative, multicenter studies of patients with documented vulvovaginal candidiasis. The studies were blinded to the point of dispensing study medication but were open thereafter. Both studies compared single administration of a miconazole nitrate (1200 mg) vaginal ovule to administration of MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream original formulation for seven consecutive nights. A tube of MONISTAT® External Vulvar Cream was also provided to patients in the miconazole nitrate (1200 mg) vaginal [redacted] groups. This was to be applied twice daily to the vulvar area, as needed for symptomatic relief, for up to seven days. For the purpose of these

Phase III studies was to determine the efficacy and safety of miconazole nitrate (1200 mg) vaginal [redacted] administered for a single night compared to the efficacy and safety of currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream original formulation administered for seven days in the treatment of women with vulvovaginal candidiasis.

The two studies were conducted at a total of 31 centers. Two centers did not enroll any patients. Subjects were enrolled at one of 29 investigative centers as outpatients and treatment was self-administered over either one or seven days. Twenty-eight of 29 investigative centers were in the United States. The remaining center was in Costa Rica. All patients were required to have clinical and microbiological confirmation of disease. Clinical confirmation required the presence of at least one of the following signs and symptoms: vulvovaginal itching, vulvovaginal burning/irritation, vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, and vaginal edema. Microbiological confirmation of vulvovaginal candidiasis required documentation of *Candida* species by both 10% KOH preparation and by BiGGY culture. Patients were seen and evaluated at admission (day 1), at Return Visit 1 (days 15-19), and at Return Visit 2 (days 35-43).

The primary efficacy variable was the overall therapeutic cure rate. An overall therapeutic cure is an overall clinical cure and an overall microbiologic cure. A patient was an overall microbiologic cure if both 10% KOH and culture were negative at both return visits. A patient was an overall clinical cure if the clinical signs and symptoms were improved at the first return visit and essentially normal/absent at the second return visit. The overall clinical and microbiological cure rates, cure rates at Return Visits 1 and 2, relapse rates and symptomatic relief were secondary efficacy parameters. A patient was considered a therapeutic cure at Return Visit 1 or 2 if she was both a microbiological cure and a clinical cure at that visit. A clinical cure was based on the improvement in vulvovaginal signs and symptoms of candidiasis that depended on the baseline severity of disease. A microbiological cure required both a negative 10% KOH and a negative BiGGY culture.

***Reviewer's Comment**: It should be noted that the secondary efficacy parameters were not specified in the protocols but only in the study reports.*

II. Efficacy Evaluation

For this review, the key primary efficacy variable for assessing the equivalence of miconazole nitrate (12000 mg) vaginal [redacted] and the currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream is the overall therapeutic cure rate. For completeness, overall clinical and microbiological cure rates are also reported. Confidence intervals based on the normal approximation of the binomial are used to assess the equivalence of the two treatment groups. In addition to this confidence

interval, a weighted confidence interval based on the investigator-stratified Mantel-Haenszel estimator of the therapeutic response rate difference is presented.

Study 96-002

- Patient Demographics

Study 96-002 had 140 patients randomized to the miconazole nitrate (1200 mg) vaginal [redacted] and 138 patients randomized to the MONISTAT® 7 group (M7C). The following table contains the demographic characteristics by treatment group for all randomized patients. As can be seen from Table 1, distributions of these variables are similar across the two treatment groups ($p > 0.39$). The descriptive variables race (white versus others) and baseline severity are evaluated using the Cochran-Mantel-Haenszel statistic stratified by investigator. Age was evaluated using ANOVA with investigator effects.

Table 1
Patient Demographics
All Randomized Patients
Study 96-002

		1200 mg	M7C	P-value
# Patients		140	138	-
Age	mean (SD)	33.9 (12.3)	32.5 (12.0)	.396
	min, max	18, 79	18, 70	
Race (N)	Caucasian	80	84	.589
	Black	21	23	
	Asian	3	3	
	Hispanic	33	24	
	Amer-Indian	1	1	
	Other	2	6	
Baseline Severity (N)				.877
	Very Mild	6	2	
	Mild	80	72	
	Moderate	47	54	
	Severe	7	10	

- Analysis Results

The results based on the sponsor's defined efficacy evaluable population are summarized below. The sponsor defined 99 patients in the miconazole nitrate (1200 mg) vaginal [redacted] group and 97 patients in the MONISTAT® 7 group as evaluable for overall efficacy. The main reasons for excluding patients from the analysis were negative or missing KOH or BiGGY culture on admission (17 1200 mg and 8 M7C), did not return for visits 1 and/or 2 (4 1200 mg and 2 M7C), use of prohibited medicine (6 1200 mg and 9 M7C), improper use of study medication (5 1200 mg and 8 M7C), and tampon use (0 1200 mg and 5 M7C).

Reviewer's Comment: *A 20% random patient selection of the data was provided to the medical officer for review. No patient evaluability or cure assessment changes were made. Therefore, the sponsor's data was accepted.*

Table 2 contains the overall clinical, microbiological, and therapeutic cure rates. These rates are slightly higher for the miconazole nitrate (1200 mg) vaginal [redacted] group. However, there is not a statistically significant difference between treatment groups in the overall therapeutic cure rate.

Table 2
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Sponsor's Efficacy Evaluable
Study 96-002

Type of Cure n(%)	1200 mg N=99	M7C N=97
Clinical	81 (81.8%)	79 (81.4%)
Microbiological	75 (75.8%)	71 (73.2%)
Therapeutic	71 (71.7%)	68 (70.1%)

The point estimate of the difference between the two treatment groups for the overall clinical, microbiological, and therapeutic cure rates and the corresponding 95% confidence intervals are summarized in Table 3. Three 95% confidence intervals are reported in Table 3; the first is the sponsor calculated confidence interval that does not include the correction factor and the second is the confidence interval that uses the Yates' continuity correction factor. The weighted 95% confidence interval is also reported for therapeutic cure. Since the lower limit of the confidence intervals lies within the lower bound of -20.0% and the confidence interval contains zero, miconazole nitrate (1200 mg) vaginal [redacted] is therapeutically equivalent to the currently marketed MONISTAT® 7. This statement also holds for clinical and microbiological equivalence.

Table 3
Difference in Overall Clinical, Microbiological, and Therapeutic Cure Rates
and Corresponding 95% Confidence Intervals
Sponsor's Efficacy Evaluable
Study 96-002

Type of Cure	Difference in Cure Rate (1200 mg-M7C)	Sponsor's 95% CI	Corrected 95% CI	Weighted 95% CI
Clinical	0.4%	(-10.5%, 11.2%)	(-11.5%, 12.3%)	-
Microbiological	2.6%	(-9.7%, 14.8%)	(-10.6%, 15.8%)	-
Therapeutic	1.6%	(-11.1%, 14.3%)	(-12.1%, 15.3%)	(-12.9%, 13.6%)

In addition to the efficacy evaluable population, a modified intent-to-treat population was analyzed by this reviewer. The modified intent-to-treat population consists of all randomized patients except those who had negative KOH or BiGGY cultures at baseline. Subjects classified as non-evaluable (indeterminate) for therapeutic cure were considered as failures in this analysis (13 1200 mg and 14 M7C). As seen in Table 4, the cure rates are lower than those seen for the evaluable population but the rates remain higher for the miconazole nitrate (1200 mg) vaginal [redacted] group and the conclusion of equivalence is still drawn. An extreme case scenario would be to consider non-evaluable 1200 mg subjects as failures and non-evaluable M7C subjects as cures. In

this scenario, the confidence interval about the difference in therapeutic cure rates would be (-21.3%, 3.7%). This confidence interval is just outside the range of claiming equivalence.

Table 4
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Modified Intent-to-Treat
Study 96-002

Type of Cure n(%)	1200 mg N=120	M7C N=129	Corrected 95% CI
Clinical	85 (70.8%)	91 (70.5%)	(-11.8%, 12.4%)
Microbiological	79 (65.8%)	83 (64.3%)	(-11.2%, 14.1%)
Therapeutic	74 (61.7%)	77 (59.7%)	(-11.0%, 14.9%)

A secondary efficacy variable stated in the sponsor's study report was symptom relief of itching and burning/irritation. This variable is defined as the first day that relief is achieved for both itching and burning/irritation. Table 5 summarizes the cumulative totals of patients who experienced relief by each of the first seven days.

Table 5
Cumulative Totals of Days to Relief of Itching and Burning/Irritation
Study 96-002

Group	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1200 mg	10	29	40	49	60	66
(n=94*)	10.6%	30.9%	42.6%	51.1%	63.8%	70.2%
M7C	9	15	33	42	55	64
(n=92*)	9.8%	16.3%	35.9%	45.7%	59.8%	69.6%

*=patients exhibiting symptoms at admission

The sponsor states that the proportion of patients experiencing relief by Day 3 is statistically significantly (p=0.025) higher in the miconazole nitrate (1200 mg) vaginal [redacted] group compared to the MONISTAT® 7 group. There was no statistically significant difference between the groups at Day 7 (p=1.0). The median time to symptom relief is 5 days for the miconazole nitrate (1200 mg) vaginal [redacted] group and 6 days for the MONISTAT® 7 group. The difference of one day in median time to relief is not statistically significantly different as assessed by the median test (p=0.317). There is no difference between groups in the overall time to relief (log rank, p=0.505).

***Reviewer's Comment**: The sponsor stated that the comparison at Day 3 was statistically significant (p=0.025). Since at least 2 comparisons were made, Day 3 and Day 7, an adjustment should be made to the significance level. Since this is a secondary parameter, the significance level for this test would be assessed at a value less than 0.05. Using a Bonferroni adjustment, this value is marginally significant. In addition, there were patients who had a recurrence of symptoms a day or two following the day of first relief of both itching and burning/irritation. If the definition of days to relief of itching and burning/irritation was redefined as the day at which relief of both itching and burning/irritation was achieved without further recurrence, there would be no*

statistically significant difference between groups at Day 3 (p=0.042) using the Bonferroni adjusted significance level. It should be noted that the sponsor calculated the median time to relief as 4 days in the ovule group and 5 days in the MONISTAT® 7 group.

Study 97-006

- Patient Demographics

Study 97-006 had 142 patients randomized to the miconazole nitrate (1200 mg) vaginal [redacted] group and 138 patients randomized to the MONISTAT® 7 group (M7C). The following table contains the demographic characteristics by treatment group for all randomized patients. As can be seen from Table 6, distributions of these variables are similar across the two treatment groups ($p > .18$). The descriptive variables race (white versus others) and baseline severity are evaluated using the Cochran-Mantel-Haenszel statistic stratified by investigator. Age was evaluated using ANOVA with investigator effects.

Table 6
Patient Demographics
All Randomized Patients
Study 97-006

		M3C	M7C	P-value
# Patients		142	138	-
Age mean (SD)		35.3 (13.5)	36.9 (13.4)	.226
min, max		17, 75	17, 76	
Race (N)	Caucasian	96	99	.396
	Black	27	25	
	Asian	5	2	
	Hispanic	13	11	
	Amer-Indian	1	0	
	Other	0	1	
Baseline Severity (N)				.181
Very Mild		2	1	
Mild		92	99	
Moderate		44	36	
Severe		3	2	

- Analysis Results

The results based on the sponsor's defined efficacy evaluable population are summarized below. The sponsor defined 104 patients in the miconazole nitrate (1200 mg) vaginal [redacted] group and 90 patients in the MONISTAT® 7 group as evaluable for overall efficacy. The main reasons for excluding patients from the analysis were negative or missing KOH or BiGGY culture on admission (9 1200 mg and 14 M7C), did not return for visits 1 and/or 2 (7 1200 mg and 8 M7C), use of prohibited medication (6 1200 mg and 4 M7C), improper use of study medication (3 1200 mg and 7 M7C), and tampon use (4 1200 mg and 4 M7C).

Reviewer's Comment: *A 20% random patient selection of the data was provided to the medical officer for review. No patient evaluability or cure assessment changes were made. Therefore, the sponsor's data was accepted.*

Table 7 contains the overall clinical, microbiological, and therapeutic cure rates. There is not a statistically significant difference between treatment groups in the overall therapeutic cure rate.

Table 7
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Sponsor's Efficacy Evaluable
Study 97-006

Type of Cure n(%)	1200 mg N=104	M7C N=90
Clinical	72 (69.2%)	63 (70.0%)
Microbiological	72 (69.2%)	62 (68.9%)
Therapeutic	64 (61.5%)	55 (61.1%)

The point estimate of the difference between the two treatment groups for the overall clinical, microbiological, and therapeutic cure rates and the corresponding 95% confidence intervals are summarized in Table 8. Three 95% confidence intervals are reported in Table 8; the first is the sponsor calculated confidence interval that does not include the correction factor and the second is the confidence interval that uses the Yates' continuity correction factor. The weighted 95% confidence interval is also reported for therapeutic cure. Since the lower limit of the confidence intervals lies within the lower bound of -20.0% and the confidence interval contains zero, miconazole nitrate (1200 mg) vaginal [redacted] is therapeutically equivalent to the currently marketed MONISTAT® 7. This statement also holds for clinical and microbiological equivalence.

Table 8
Difference in Overall Clinical, Microbiological, and Therapeutic Cure Rates
and Corresponding 95% Confidence Intervals
Sponsor's Efficacy Evaluable
Study 97-006

Type of Cure	Difference in Cure Rate (1200 mg-M7C)	Sponsor's 95% CI	Corrected 95% CI	Weighted 95% CI
Clinical	-0.8%	(-13.7%, 12.2%)	(-14.8%, 13.2%)	-
Microbiological	0.3%	(-12.7%, 13.4%)	(-13.8%, 14.4%)	-
Therapeutic	0.4%	(-13.3%, 14.2%)	(-14.4%, 15.2%)	(-16.4%, 12.4%)

In addition to the efficacy evaluable population, a modified intent-to-treat population was analyzed by this reviewer. The modified intent-to-treat population consists of all randomized patients except those who had negative KOH or BiGGY cultures at baseline. Subjects classified as non-evaluable (indeterminate) for therapeutic cure were considered as failures in this analysis (20 1200 mg and 19 M7C). As seen in Table 9, the cure rates are lower than those seen for the evaluable population but the conclusion of equivalence is still drawn. An extreme case scenario would be to consider

non-evaluable 1200 mg subjects as failures and non-evaluable M7C subjects as cures. In this scenario, the confidence interval about the difference in therapeutic cure rates would be (-24.3%, 1.5%). This confidence interval is outside the range of claiming equivalence.

Table 9
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Modified Intent-to-Treat
Study 97-006

Type of Cure n(%)	1200 mg N=132	M7C N=122	Corrected 95% CI
Clinical	76 (57.6%)	70 (57.4%)	(-12.8%, 13.2%)
Microbiological	78 (59.1%)	66 (54.1%)	(-8.0%, 18.0%)
Therapeutic	68 (51.5%)	59 (48.4%)	(-9.9%, 16.3%)

A secondary efficacy variable stated in the sponsor's study report was symptom relief of itching and burning/irritation. This variable is defined as the first day that relief is achieved for both itching and burning/irritation. Table 10 summarizes the cumulative totals of patients who experienced relief by each of the first seven days.

Table 10
Cumulative Totals of Days to Relief of Itching and Burning/Irritation
Study 97-006

Group	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1200 mg (n=100*)	14 14.0%	41 41.0%	51 51.0%	58 58.0%	63 63.0%	66 66.0%
M7C (n=85*)	7 8.2%	19 22.4%	31 36.5%	39 45.9%	52 61.2%	59 69.4%

*=patients exhibiting symptoms at admission

The sponsor states that the proportion of patients experiencing relief by Day 3 is statistically significantly (p=0.008) higher in the miconazole nitrate (1200 mg) vaginal [redacted] group compared to the MONISTAT® 7 group. There was no statistically significant difference between the groups at Day 7 (p=0.64). The median time to symptom relief is 4 days for the miconazole nitrate (1200 mg) vaginal [redacted] group and 6 days for the MONISTAT® 7 group. The difference of two days in median time to relief is not statistically significantly different as assessed by the median test (p=0.075). There is no difference between groups in the overall time to relief (log rank, p=0.580).

***Reviewer's Comment**: The comparison at Day 3 is statistically significant (p=0.008) at the Bonferroni adjusted significance level as discussed in a Reviewer's Comment in Protocol 96-002. However, using the redefined days to relief described previously in a Reviewer's Comment in Protocol 96-002, there is not a statistically significant difference between treatment groups (p=0.310). It should be noted that the sponsor calculated the median time to relief as 3 days in the ovule group and 4 days in the MONISTAT® 7 group.*

Subset Analysis

To investigate differences among demographic subsets, subgroups of patients were formed by race (white vs. others) and age (≤ 45 vs. ≥ 46, age was rounded to the closest year). Since all subjects are females, a subset analysis by gender is not necessary and the age division was chosen to see if a difference between perimenopausal and postmenopausal females exists. The data defined by the sponsor as valid for overall efficacy in Study 96-002 and Study 97-006 were pooled by this reviewer to provide a larger sample size for this exploratory analysis. For each subset, overall therapeutic cure rates were compared for each treatment group. There are no statistically significant differences in the overall therapeutic cure rates for any subset. Females age 45 or less have higher overall therapeutic cure rates than females 46 and older. Table 11 includes the overall therapeutic cure rates by each subset variable.

Table 11
Overall Therapeutic Cure Rates by Subset
Pooled Studies 96-002 and 97-006

1200 mg	M7C	P-value	1200 mg	M7C	P-value
White			*Non-White*		
(N=127)	(N=125)		(N=76)	(N=62)	
85 (66.9%)	84 (67.2%)	.964	50 (65.8%)	39 (62.9%)	.725
≤45			*≥46*		
(N=157)	(N=141)		(N=46)	(N=46)	
110 (70.1%)	97 (68.8%)	.812	25 (54.4%)	26 (56.5%)	.834

III. Safety Evaluation

The following is an analysis of the safety data provided by the sponsor. Since Protocol 96-002 and Protocol 97-006 are similarly designed, the data of the two studies is pooled to allow for larger sample sizes. Table 12 summarizes the reported adverse events in the two studies. The total number of patients valid for safety, the number and percent of patients with at least one reported adverse event, the total number of adverse events reported, and the number and percent of adverse events that were considered possibly, probably, or highly probably related to study drug are included in the table for miconazole nitrate (1200 mg) vaginal [redacted] and MONISTAT® 7.

Table 12
Adverse Events
Protocols 96-002 and 97-006 Combined

	1200 mg	M7C
Total # Patients Valid for Safety	272	265
# (%) Patients with AE	191 (70.2%)	170 (64.2%)
Total # AEs Reported	517	465
# (%)Related AE's	171 (33.1%)	152 (32.7%)

Note: Related corresponds to possibly, probably, or highly probably related.

Overall, safety is comparable between the two treatment groups. Adverse events were reported by about two-thirds of women in each treatment group. The miconazole nitrate (1200 mg) vaginal [redacted] group reported slightly more adverse events than the MONISTAT® 7 group. However, similar amounts of the adverse events were considered related to study drug. The majority of the related adverse events for both groups were pain, irritation, burning, or pruritus of the female genitalia.

Adverse events reported by more than 2% of patients in either treatment group are summarized in Table 13.

Table 13
Adverse Events Reported by > 2% of Patients
Protocols 96-002 and 97-006 Combined

Adverse Event	1200 mg (N=272)	M7C (N=265)
Pruritus, external female genitalia	52 (19.1%)	71 (26.8%)
Burning, female genitalia	71 (26.1%)	63 (23.8%)
Irritation, female genitalia	55 (20.2%)	41 (15.5%)
Headache	48 (17.6%)	50 (18.9%)
Discharge, female genitalia	28 (10.3%)	12 (4.5%)
Erythema, female genitalia	13 (4.8%)	13 (4.9%)
Upper Respiratory Infection	13 (4.8%)	9 (3.4%)
Cramps, GI	13 (4.8%)	6 (2.3%)
Dysmenorrhea	9 (3.3%)	12 (4.5%)
Pharyngitis	11 (4.0%)	7 (2.6%
Pain, trunk	5 (1.8%)	9 (3.4%)
Edema, female genitalia	9 (3.3%)	8 (3.0%)
Nausea	7 (2.6%)	4 (1.5%)
Infection, urinary tract	7 (2.6%)	0 (0.0%)
Excoriation/abrasion, female genitalia	3 (1.1%)	6 (2.3%)
Vaginitis	2 (0.7%)	6 (2.3%)
Dysuria	6 (2.2%)	5 (1.9%)
Sinusitis	6 (2.2%)	2 (0.8%)
Pain, female genitalia	6 (2.2%)	1 (0.4%)
Insomnia	6 (2.2%)	1 (0.4%)

IV. Conclusions

Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

1. *Based on the efficacy analyses performed, miconazole nitrate (1200 mg) vaginal [redacted] administered once has been shown to be therapeutically equivalent to the currently marketed MONISTAT® 7.*

2. *Overall, safety is comparable between the two treatment groups. Adverse events were reported by about two-thirds of women in each treatment group. The miconazole nitrate (1200 mg) vaginal [redacted] group reported slightly more adverse events than the MONISTAT® 7 group. However, similar amounts of the adverse events were considered related to study drug. The majority of the related adverse events for both groups were pain, irritation, burning, or pruritus of the female genitalia.*

3. *Statements regarding symptom relief should be removed from the label for the following reasons:*
   - *this secondary variable was not specified in the protocol,*
   - *statistical significance is only marginal in one protocol when using a Bonferroni adjusted significance level and there is no statistical significance in either protocol with a refining of the definition to not allow a recurrence of symptoms,*
   - *the difference in the median time to relief is not statistically significant.*

/S/ 4/15/99
Cheryl Dixon, Ph.D.
Biostatistician, DOB III

Concur: /S/ 4/15/99
Nancy Silliman, Ph.D.
Team Leader, DOB III

cc:
Archival NDA 20-968 Monistat 1 Dual-Pak
HFD-590
HFD-590/ Dr. Goldberger
HFD-590/ Dr. Albrecht
HFD-590/ Dr. Leissa
HFD-590/ Dr. Cox
HFD-590/ Dr. Chi
HFD-725/ Dr. Huque
HFD-725/ Dr. Silliman
HFD-725/ Dr. Dixon
Chron.

APPEARS THIS WAY
ON ORIGINAL

This review contains 11 pages.