CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

MICROBIOLOGY REVIEW(S)

Microbiology Review

Division of Special Pathogens and Immunologic Drug Products

(HFD-590)

NDA# 20-827

Reviewer : Linda Gosey
Correspondence Date : 3-31-97
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Review Complete Date: 3-20-98

Sponsor: Advanced Care Products
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PO Box 6024
N. Brunswick, New Jersey 08902

Submission Reviewed: Original (3-31-97); supplement BL (10-7-97);

Drug Category: Antifungal

Indication: Treatment of vaginal Candidiasis

Dosage Form: Vaginal cream

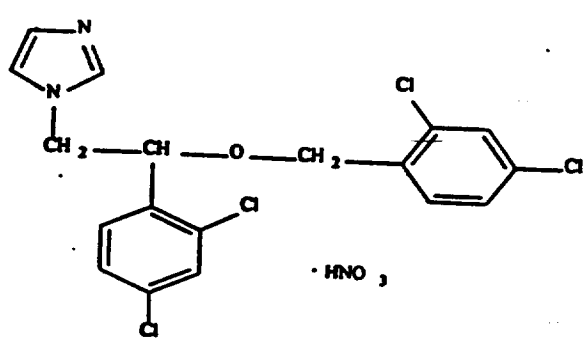
Product Names:

a. Proprietary: Monistat nitrate (4%) cream

b. Nonproprietary: Miconazole

c. Chemical: 1-[2,4-dicholoro-B-[(2,4-dichlorobenzyl) oxyl]phenethyl]imidazole nitrate

Structural Formula:



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Supporting Documents: NDA 17-450; NDA 18-520; NDA 18-888; NDA 18-592; NDA 20-288; NDA 20-670

Background:

Drug: 4% Miconazole Nitrate cream

Miconazole nitrate was first approved in 1974 as a vaginal cream (2%, 100 mg) to be dosed daily for 7 days for the treatment of vaginal candidiasis. Subsequently, approvals have been given for miconazole nitrate formulated as a vaginal suppository (100 and 200 mg) and tampon (200 mg). Recently, all of the above mentioned formulations have been approved for over the counter (OTC) use in the United States. This NDA contains data from two clinical trials in which the efficacy of a 3 day treatment regimen with 4% miconazole nitrate cream (new base formulation) was compared to the 7 day treatment regimen with 2% miconazole nitrate cream in the old base formulation.

Disease: Vulvovaginal Candidiasis:

The intended use of this OTC product is for the treatment of occasional and recurrent episodes ($\leq$4 infections/year) of vulvovaginal candidiasis. To fully comprehend the extent of this disease several factors must be taken into account; the type of infection produced, the fungal pathogen producing the infection, the susceptibility patterns of the fungal pathogens to the antifungal agent, the immunologic status of the host and other factors that may predispose the patient to a fungal infection.

Vulvovaginal candidiasis (VVC) can be divided into three basic categories. Subjects who periodically have VVC are categorized in this review as having occasional episodes of VVC. Women with recurrent infection can have up to 4 episodes per year. Subjects with chronic VVC have frequent outbreaks of severe VVC that usually requires long term antifungal therapy (#1). These patients are generally immunosuppressed or are taking other drugs that can predispose them to developing VVC.

Factors that predispose women to recurrent or chronic VVC include: diabetes, long term steroid or antibiotic use and immunosuppression (e.g. AIDS, organ transplant patients, etc.). Other factors that may increase the risk of developing recurrent or chronic disease are the severity and duration of each episode of vaginal candidiasis, as well as the period of time between episodes of symptomatic vulvovaginal candidiasis (#2,#3). In HIV positive women as many as 45% have experienced

recurrent vulvovaginal candidiasis (RVVC) (#4). In many cases RVVC is the initial illness seen in HIV positive women and may occur even when CD4 counts are >500 cells/mm3 (#5). In addition, recent studies have shown that prophylactic fluconazole therapy for esophageal candidiasis in this population has lead to an increased incidence of fluconazole resistant strains of *Candida albicans* in the esophagus, as well as an increase in the incidence of esophageal and vaginal tract infections due to non-albicans strains of fungi (#6).

Oncology and bone marrow transplant patients are also at high risk for developing fluconazole resistant strains of *C. albicans* and non-albicans strains of fungi. The incidence of these infections has increased over the past decade due to the expanded use of fluconazole prophylactic therapy during neutropenic episodes.

The incidence of VVC in the United States has nearly doubled from 1980 to 1990. This rise appears to be associated with the increased use of vaginal antifungal agents. Not only have infections due to *C. albicans* increased but the incidence of VVC due to non-albicans yeasts has more than doubled from 5-10% in the 1980's to as high as 23% in the 1990's (#7). The most common non-albicans strains of yeast producing VVC are *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis*. These fungal strains are inherently more resistant to the antifungal azoles thus making the treatment of these infections more difficult (#8). Suboptimal treatment of the non-albicans strains has resulted in more frequent episodes of severe VVC.

Summary:

Preclinical Microbiology Review:

In this NDA the sponsor is seeking approval of miconazole nitrate (4%, 200 mg) in a newly formulated base cream as a 3 day treatment regimen for vaginal candidiasis. In examining the preclinical microbiology section of the document it was noted that the sponsor did not submit any in vitro or in vivo information regarding the activity of miconazole against Candida species. Because miconazole is already approved for the treatment of vaginal candidiasis it is not necessary to conduct another formal microbiology review of the preclinical activity data. However, there are several microbiologic concerns that will be brought up in this review that may have an impact on the labeling of this new treatment regimen.

Clinical Studies:

The approval of this new drug product required the demonstration of efficacy equivalence and bioequivalence between a 3 day treatment course with 4% miconazole nitrate cream (new base formulation) and a 7 day treatment course with 2% miconazole nitrate (old base formulation). To demonstrate equivalence the sponsor conducted a single pharmacokinetic study and two clinical efficacy trials.

Protocol 95-009-P: Pharmacokinetic Study

To accurately characterize the effects of the 4% miconazole nitrate vaginal cream the sponsor first determined if the new base cream formulation affected the pharmacokinetics of miconazole and/or produced greater irritability to the vaginal mucosa. Either of these affects could have an impact on the overall microbiologic activity of this product. The currently marketed cream base contains benzoic acid, butylated hydroyanisole, mineral oil, peglicol 5 oleate, pegoxol 7 and purified water. The new base formulation contains benzoic acid, cetyl alcohol, stearyl alcohol, isopropyl myristate, propylene glycol, polysorbate 60, potassium hydroxide and purified water.

In study 95-009 the absorption and pharmacokinetic characteristics of 2% and 4% miconazole nitrate in a new base cream formulation were assessed and compared to the currently marketed 2% miconazole cream (old formulation). Miconazole levels were determined in the serum at 0, 2, 3, 8, 12, 16, and 24 hours following the first dose and at 0, 2, 4, 8, 12, 16, 24, 36, 48, and 72 hours after the last dose. These test results will be reviewed by the Division's pharmacologist and the biopharmacology reviewer. However, there is concern that the systemic levels of miconazole that result with the new formulation may contribute to the development of drug resistant fungal infections in immunosuppressed women with recurrent VVC.

To determine the potential for drug resistance development it was necessary to first correlate systemic drug levels to miconazole MICs for the various Candida species. In the submission the sponsor noted that Cmax levels were increased more than 3-fold, 6.8 ug/L versus 2.0 ug/L, in patients receiving the 2% miconazole nitrate new formulation compared to subjects receiving 2% miconazole nitrate cream in the old formulation (see tables 1 and 2). The peak concentration for a single and 3 day multiple dose of 200 mg miconazole (4%, new

formulation) was 9.4 ug/L and 12.68 ug/L, respectively. These data show that the systemic levels of miconazole achieved with the proposed formulation are substantially higher than the Cmax levels obtained with the 2% miconazole cream in either base formulation (See tables 1 and 2).

Table 1

Pharmacokinetic Results Following Initial Study Drug Dose

Treatment Group	Study Statistic	AUC (ug/L.h)	Cmax (ug/L)	Tmax (Hours)
Miconazole Nitrate 3-Day N=14	Mean	136.04	9.480	12.286
	STD	45.748	2.9221	2.9202
	Range			
MONISTAT® 7 (New base) N=14	Mean	91.43	6.812	10.571
	STD	35.345	2.3626	1.9890
	Range			
MONISTAT® 7 (Marketed) N=14	Mean	32.09	1.993	12.286
	STD	8.302	0.4603	4.2864
	Range			
Cross Reference: TABLE 2A and Tabulation 8A, pages 29 and 183 respectively.				

Table 2

Pharmacokinetic Results Following Final Study Drug Dose

Treatment Group	Study Statistic	AUC (ug/L.h)	Cmax (ug/L)	Tmax (hours)
Miconazole Nitrate 3-Day N=14	Mean	365.64	12.678	12.571
	STD	183.132	4.4148	3.4578
	Range			
MONISTAT® 7 (New Base) N=14	Mean	241.47	8.840	10.000
	STD	118.227	2.9553	2.0755
	Range			
MONISTAT® 7 (Marketed) N=14	Mean	82.76	2.535	10.286
	STD	28.437	0.5767	3.0237
	Range			
Cross Reference: TABLE 2B and Tabulation 8B, pages 30 and 186 respectively.				

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To directly compare systemic levels of miconazole to MICs it was necessary to convert the Cmax values from ug/L to ug/ml by dividing by 1000. Thus the miconazole Cmax levels at 24 hours were .002, .0068 and .0094 ug/ml in patients receiving 2% miconazole in the old base, 2% miconazole in the new base and 4% miconazole in the new base formulation, respectively. Six days after the multiple dose regimen was initiated (e.g. 3 days of dosing and 3 days post treatment) the Cmax level for the 4% cream was 0.013 ug/ml. These data indicate that for approximately one week the concentration of miconazole in the blood was around 0.01 ug/ml. This level approaches the MIC_{50} value for susceptible *C. albicans* species (Fig. 1).

Fig. 1

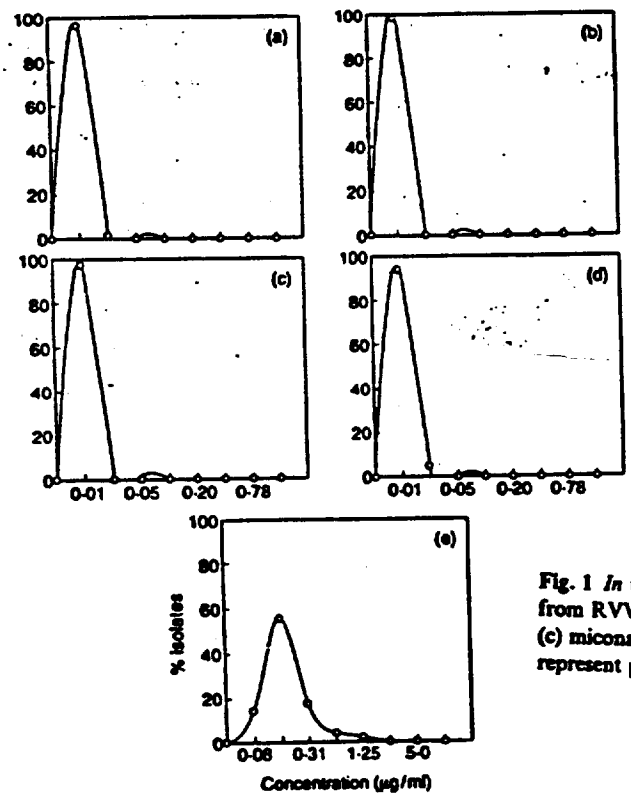

Fig. 1 *In vitro* susceptiblity of 177 vaginal *C. albicans* isolates from RVVC patients to (a) ketoconazole, (b) clotrimazole, (c) miconazole, (d) itraconazole and (e) fluconazole. Graphs represent percentage isolates with given MIC versus $\mu g\ ml^{-1}$ drug.

Protocols 95-005-P and 95-007-P: Efficacy studies

The design of these two efficacy trials were similar. Both studies were double-blind, randomized, controlled, parallel group, comparative phase III trials in female patients with documented vulvovaginal candidiasis. Clinical trials 95-005-P and 95-007-P were conducted to compare the safety and efficacy of miconazole nitrate, 4% vaginal cream (3 day treatment) to the approved 2% miconazole nitrate cream, a 7 day treatment regimen. In protocol 95-007-P there was a third treatment arm, 2.8% miconazole nitrate cream for 5 days. However, these data will not be evaluated in this NDA. According to the sponsor they will be reported in a separate submission at a later date.

In both studies patients were seen on an outpatient basis with treatment being self-administered. Prior to entering the study patients had to be clinically symptomatic and have microbiologically confirmed disease. Microbiologic confirmation consisted of both a positive potassium hydroxide (KOH) preparation and a positive fungal culture. All patients were evaluated on three occasions; at admission (visit 1 - V1), 8-10 days after completion of treatment (return visit 1 - RV1) and 30-35 days after the completion of treatment (return visit 2-RV2).

In both studies the parameter used to determine overall efficacy was therapeutic cure. Clinical cure and microbiologic cure were independently evaluated in the studies. As previously noted therapeutic cure was the composite of both the clinical and microbiologic effects (See table 3).

Table 3

ASSESSMENT OF THERAPEUTIC CURE

Clinical Cure	Microbiologic Cure	Therapeutic Cure
Cure	Cure	Cure
Cure	Failure	Failure
Cure	Indeterminate	Indeterminate
Failure	Cure	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Cure	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

In the protocol design microbiologic results were determined from the combined results of both the KOH preparation and the fungal culture. Patients classified as a microbiologic cure had to have both a negative KOH and fungal culture. If either test result was missing then that patient was categorized as indeterminate unless the other test result would have classified them as a failure.

A KOH preparation and a fungal culture, using the BiGGY agar as the primary isolation medium, were conducted on all vaginal specimens at the local laboratory. KOH preparations were interpreted as "positive" or "negative" for fungal elements (i.e. yeasts or pseudohyphae), however, a description of the fungal elements seen on KOH was not noted. For the fungal cultures specimens were inoculated onto BiGGY (bismuth, glucose, glycine, yeast extract agar) plates and incubated at [redacted] On this medium growth of brown to black colonies is indicative of Candida species. Culture results were recorded as "Positive" or "Negative" indicating growth or no growth of fungi, respectively. The quantity of fungi grown was not noted in these studies. Subcultures of fungal isolates were sent to the [redacted] for speciation. At the reference laboratory a germ tube test was performed to identify *Candida albicans* species. Additional biochemical tests [redacted] were used to speciate all fungi that were germ tube negative.

The Sponsor's results from clinical trial 95-005-P:

Tables 4 and 5 show the sponsor's analysis of the clinical, microbiologic and therapeutic cure rates for patients enrolled in trial 95-005-P. At return visit 1 (RV1) and return visit 2 (RV2) the cure rates in all categories (i.e. clinical, microbiologic and therapeutic) were higher in patients treated with 4% miconazole in the new base formulation versus patients receiving the marketed 2% miconazole cream. At return visit 2 (30-35 days post treatment) 67% versus 59% of the patients receiving 4% and 2% miconazole cream, respectively, were classified as a therapeutic cure (p=0.422). The microbiologic cure rates at RV2 were 72% and 65% for patients receiving the 4% and 2% miconazole nitrate creams, respectively.

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Table 4

Study 95-005-P - Clinical, Microbiological and Therapeutic Cure Rates at Return Visit 1- Patients Evaluable at Return Visit 1

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
Clinical Cure	90/97 (93%)	84/96 (88%)
Microbiological Cure	85/97 (88%)	77/96 (80%)
Therapeutic Cure	83/97 (86%)	71/96 (74%)

Table 5

Table V
Study 95-005-P - Overall Clinical, Microbiological and Therapeutic Cure Rates
Return Visit 2

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
Clinical Cure	67/87 (77%)	61/88 (69%)
Microbiological Cure	63/87 (72%)	57/88 (65%)
Therapeutic Cure	58/87 (67%)	52/88 (59%)

The sponsor evaluation of clinical trial 95-007-P:

Tables 6 and 7 show the sponsor's assessment of the cure rates for patients evaluated at return visit 1 and at the end of clinical trial 95-007-P, RV2. At RV1 the therapeutic cure rate for patients receiving miconazole 4% and 2% creams were 75% and 79%, respectively. At the end of this study (RV2) the therapeutic cure rates dropped to 58% and 63% for subjects receiving 4% and 2% miconazole cream (p=0.478). The overall microbiologic cure rates for patients receiving the 4% miconazole nitrate cream and the 2% cream were 62% and 66%, respectively.

It is of interest to note that in both studies the cure rates decreased between RV1 and RV2 irrespective of the treatment arm. The exact reason for this decrease in cure rates over time cannot be explained. However, factors such as patients dropping out of the study between the two visit times, relapse of disease or recolonization of yeast in the vagina one month post therapy could have impacted on the apparent decrease in cure rates seen at RV2.

Table 6

Study 95-007-P - Clinical, Microbiological and Therapeutic Cure Rates at Return Visit 1 - Patients Evaluable at Return Visit 1

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
Clinical Cure	96/104 (92%)	99/107 (93%)
Microbiological Cure	80/104 (77%)	86/107 (80%)
Therapeutic Cure	78/104 (75%)	84/107 (79%)

For Return Visit 1 therapeutic response the estimated odds ratio is 0.80, and a point estimate of the difference in cure rates is -3.5%.

Table 7

Study 95-007-P - Overall Clinical, Microbiological and Therapeutic Cure Rates

Return Visit 2

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
Clinical Cure	65/98 (66%)	70/100 (70%)
Microbiological Cure	61/98 (62%)	66/100 (66%)
Therapeutic Cure	57/98 (58%)	63/100 (63%)

For overall therapeutic response the estimated odds ratio is 0.78, and a point estimate of the difference in cure rates is -4.84%.

Comments:

During the review of this NDA several microbiologic concerns and considerations emerged. These issues pertained to the design of the clinical trials and the clinical and microbiologic data obtained from studies 95-005 and 95-007. Below is a detailed discussion of each concern.

1. There is concern regarding the systemic level of miconazole that is obtained when patients use this product to treat a vaginal infection. As previously stated the Cmax obtained from 4% miconazole, new base cream, is approximately 0.01 ug/ml. This systemic level of miconazole is comparable to miconazole MIC_{50}s for *C. albicans* species (≤ 0.01 ug/ml) (#9). It is anticipated that the observed systemic levels of miconazole will not present a problem in immune competent women if the product is used as anticipated (≤4 times per year). However,

there are concerns if specific patient populations (i.e. immunosuppressed women) use this product more frequently than intended.

As noted previously, immunosuppressed patients (i.e. AIDS, organ transplant patients, and patients on long term steroid or antibiotic therapy) are at high risk for developing chronic VVC. Chronic VVC is generally severe and requires long term treatment. While the label cautions against chronic use it is anticipated that some women who have chronic VVC may opt for self-treatment due to ease of access (i.e over-the-counter (OTC)). The prolonged use of vaginal miconazole may potentially predispose these subjects to more severe fungal infections in several ways. First, overuse of vaginal miconazole may potentially lead to more serious vaginal infections due to naturally resistant strains of fungi (i.e. *C. glabrata, C. krusei. C. parapsilosis* and *C. tropicalis*), as well as potentially creating miconazole resistant strains of *C. albicans*.

The second issue of concern is cross resistance. Azole resistant strains of *C. albicans* can develop when long term fluconazole treatment or prophylactic therapy is administered. Fungal isolates that have developed fluconazole resistance have also shown cross resistance to ketoconazole and sometimes itraconazole. Because the mechanism of action is the same for both the topical and systemic antifungal azoles, it is highly probable that fungal isolates that develop resistance to miconazole may also develop resistance to the other vaginal antifungal azoles (i.e. clotrimazole, butoconazole, etc.), as well as the systemic azole antifungals.

Finally, there is the concern that systemic levels of miconazole may place immunosuppressed women at risk for developing fungal infections at other sites (e.g. the oropharynx or esophagus) due to inherently resistant strains of Candida. It has been observed that HIV positive women receiving long term azole prophylaxis for oropharyngeal Candidiasis have an increased incidence of oropharyngeal and vaginal infections due to non-albicans strains of yeasts which are inherently resistant to fluconazole and other azoles (#6). Thus, if 4% vaginal miconazole cream is used frequently to treat chronic VVC there is a hypothetical concern that sustained low level exposure to drug may induce drug resistance in azole susceptible *C. albicans* strains normally found in the oral cavity. Alternatively, susceptible strains may be replaced by inherently resistant strains of yeasts. In either case treatment of Candidiasis in the oropharynx would then become

more difficult. It is impossible to address these questions with the information available in this NDA. However, future studies are warranted to address these concerns.

2. The overall microbiologic work up of fungal cultures in studies 95-005 and 95-007 is appropriate (i.e. isolation of the fungus, use of the germ tube test to differentiate *C. albicans* from other fungal species, and the commercial biochemical test systems employed to identify non-albicans strains). However, there is a concern regarding the suitability of BiGGY agar as the primary isolation medium. To address this issue the sponsor supplied a copy of an article by Nickerson, 1953, "Reduction of inorganic substances by yeasts". The article discusses the growth characteristics of Candida species on BiGGY agar. In the article the investigator demonstrated that most strains of *C. albicans, C. tropicalis, C. krusei, C. parapsilosis* and *C. pseudotropicalis* grew as brown to black colonies on this medium. However, mutant strains of *C. albicans* did not produce a black pigment. In addition, *T. glabrata* strains were not tested on this medium.

The relevance of these data with respect to VVC seen in today's patient populations are questionable as the paper was published more that 40 years ago. Clinical isolates producing VVC in today's patient population (specifically, azole resistant strains of *C. albicans* and *T. glabrata*) have not been adequately tested on this medium. As a consequence, it is possible that clinically significant strains of fungi may have been missed due to suboptimal recovery or frank incompatibility with the BiGGY agar. At this time nothing can be done with respect to the microbiologic data obtained from these clinical trials. However, it is highly recommended that in future clinical studies BiGGY agar not be used as the primary isolation medium for the recovery of yeasts until additional tests are performed demonstrating adequate growth of clinically relevant fungal pathogens, specifically azole resistant *C. albicans* and *T. glabrata* species.

3. The third issue pertains to the definitions used to classify patients as a microbiologic cure, failure or indeterminant. As defined in the protocol microbiologic results were determined from the combined results of both the KOH preparation and the fungal culture. The definitions for microbiologic cure and failure are acceptable when both test results are in agreement. However, several issues arise when the KOH and fungal culture are discordant or one test result is missing. The protocol stipulates that if either test result was missing then that patient was categorized as indeterminate unless the other test

result would have classified them as a failure. This definition is problematic. First there is the point that fungal cultures are more specific and objective than KOH results which are subjective and less sensitive than culture results. As a consequence, more weight should have been placed on culture results compared to KOH findings when classifying the overall microbiologic response. The second issue arises when only KOH results (i.e. fungal cultures were not done or results were missing) were used to classify the microbiologic response. Subjects who had only a positive KOH at RV1 or RV2 were categorized as a failure. However, if the KOH was negative the patient was classified as indeterminant. This categorization of patients biases towards more failures using the least sensitive test where interpretation of results is subjective.

4. The final microbiologic concern pertains to the lower cure rates found at RV2 versus RV1. The lower cure rates at the end of the study may be the result of the lack of follow up data on all patients after RV1 or the inappropriate classification of patients that were initially cured at RV1 but had a positive fungal culture or KOH preparation at RV2. In this situation differentiating colonization versus relapse becomes an issue. Colonization of Candida in the vaginal tract is generally defined as a scant to light amount of *C. albicans* in the presence of normal bacterial flora (#10, #11). Approximately 15-20% (range 10-55% depending on the sub-population of women studied) of normal or asymptomatic women are colonized with *C. albicans* (#12). The original protocol design made no provisions for differentiating colonization versus reinfection. The results of semi-quantitative fungal cultures coupled with clinical signs and symptoms may have facilitated differentiation of colonization from relapse/reinfection. Thus women who were initially cured of VVC at RV1 and had a positive fungal culture or KOH at RV2 may have been microbiologically cured of the infection and then recolonized, but classified as a microbiologic failure.

Because of these issues an independent assessment of the microbiologic results from studies 95-005 and 95-007 were conducted to determine the microbiologic cure rates for patients receiving 2% or 4% miconazole nitrate cream. Fungal culture results were used as the definitive microbiologic response as they are the most objective and sensitive microbiologic test. All fungi from positive cultures had to be identified to the species level to be considered interpretable. The KOH preparation results were viewed as supportive data. Table 8 illustrates the definitions of microbiologic response.

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Table 8

FDA's Definitions for Microbiologic Response Employing Fungal Culture Results

V1	RV1	RV2	Definition
+	+	N	Failure
+	-	+	Indeterminant
+	-	N	Non-evaluable
+	-	-	Cure
+	N	N	Non-evaluable
-/N	+/-/N	+/-/N	Non-evaluable

(+), positive fungal culture with species identification; (-), negative fungal culture; (N), fungal culture and/or yeast species identification not done or missing.

Microbiologic data sets from each patient were individually assessed. For a data set to be considered complete it was necessary to have culture results, KOH data was not sufficient, at all 3 visits excepts for patients that failed at RV1. In this case patients were discontinued from the study at RV1 and fungal cultures were not taken at RV2. Data sets were considered microbiologically "non-evaluable" if one of the following scenarios occurred; no yeasts were isolated or identified at V1, no fungal cultures were taken or results were not reported at RV1 or RV2. These patients were dropped from the total data set. Table 9 shows the number of patients that were dropped from the Division's analysis of the microbiologic data. It should be noted that only microbiologic data were evaluated in this analysis. Clinical factors or responses per the protocol design that defined a patient as non-evaluable (e.g. a patient seen outside the window of time for any visit) were not considered in this analysis.

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Table 9

FDA's assessment of the Non-evaluable Patients in Studies 95-005 and 95-007

Study	95-005		95-007	
Treatment	Miconazole 4%	Nitrate 2%	Miconazole 4%	Nitrate 2%
# of Patients				
Total # Pts with culture results at V1	138	138	142	142
# Pts with (-) cultures at V1	27	29	42	35
No follow up at RV1 and RV2	9	12	9	10
Pts (-) at RV1 with no RV2 data	15	14	14	15
Total # of evaluable Pts	87	83	77	82

Pts = patients; V1 = initial visit; RV1 = return visit 1; RV2 = return visit 2; (-) = negative fungal culture; (+) = positive fungal culture with species identification.

The percentage of patients with evaluable fungal culture data at RV2 in study 95-005 and 95-007 were 62.3%, 51.2% and 54.2%, 57.7% in the 3 day and 7 day treatment arms, respectively. The sponsor did not perform a comparable analysis to determine the percentage of patients that were microbiologically evaluable.

Patients with adequate fungal culture data were further analyzed to determine the cure and failure rates, as well as the prevalence of various fungal species in each treatment regimen. For this analysis microbiologic responses were classified as, cure, failure, conversions and non-interpretable. Patients were considered a microbiologic cure if the infecting yeast at V1 was identified to the species level and fungal cultures at RV1 and RV2 were both negative. Microbiologic failures were patients that had the same fungal species at V1 and RV1. A subset of the failures were classified as "conversions" if the fungal isolate at RV1 or RV2 was a different species from the isolate initially recovered from the

patient at V1. Patient results were categorized as "non-interpretable" if there was a positive culture at V1, a negative culture at RV1 and positive culture at RV2. These results were non-interpretable because colonization could not be differentiated from relapse with the available information. Table 10 shows the FDA's analysis of the microbiologic responses for Evaluable patients in studies 95-005 and 95-007.

Table 10

FDA's Assessment of Microbiologic Results of Evaluable Patients in Studies 95-005 and 95-007

Study	95-005		95-007	
Treatment Regimen # Patients (%)	Miconazole 4%	Nitrate 2%	Miconazole 4%	Nitrate 2%
Total # evaluable pts	87	83	77	82
Cures	64 (73.6)	61 (73.5)	49 (63.6)	61 (74.4)
C. albicans	61	60	47	58
T. glabrata	0	0	1	1
C. parapsilosis	0	1	0	1
C. krusei	2	0	0	0
C. lusitaniae	1	0	0	0
C. species	0	0	1	1
Failures	11 (12.6)	10 (12.0)	13 (16.9)	10 (12.2)
C. albicans	9	5	10	9
T. glabrata	2	4	3	0
C. tropicalis	0	0	0	1
C. krusei	0	1	0	0

Table 10 (cont)

Conversions at RV1 or RV2	**1 (1.2)**	**4 (4.8)**	**3 (3.9)**	**1 (1.2)**
C. alb > T. glab	0	2	2	0
C. alb > T. candida	0	0	0	1
C. alb > C. parap	0	0	1	0
C. alb > C. krusei	0	1	0	0
C. alb > Monilia sp.	1	0	0	0
T. glab > C. alb	0	1	0	0
Non-interpretable +V1> -RV1 >+RV2	**11 (12.6)**	**8 (9.6)**	**12 (15.6)**	**10 (12.2)**
C. alb> - >C. alb	11	6	11	9
T. glab> - >T. glab	0	0	1	0
C. parap> - >C. parap	0	1	0	0
C. trop> - >C. trop	0	1	0	0
S. cerv> - >S. cerv	0	0	0	1

V1 = visit 1; RV1 = return visit 1; RV2 = return visit 2; + = positive fungal culture; - = negative fungal culture; C. alb = Candida albicans; T. glab = Torulopsis glabrata; C. parap = Candida parapsilosis; C. trop = Candida tropicalis; S. cerv = Saccharomyces cerevisiae;

The FDA's analysis of study 95-005 showed equivalence in the microbiologic cure rates (74% and 74%) of subjects treated with 4% and 2% miconazole nitrate versus the sponsor's microbiologic cure rates of 72% and 65%, respectively. However, in study 95-007 the overall microbiologic cure rates for patients receiving the 4% miconazole nitrate cream and the 2% miconazole cream as determined by the sponsor and the FDA were (62% and 66%) and (64% and 75%), respectively. In the FDA's analysis a higher microbiologic cure rate was seen in control arm.

The cure and failure rates of particular fungal strains following treatment with the 2% or 4% miconazole nitrate cream was also determined. The data show that the majority of the failures were due to *C. albicans* and *T. glabrata* strains. To determine the cure and failure rates for the various fungal species the number of isolates falling into these categories in the two studies were combined. A total of 19/127 (15%) and 14/132 (10.6%) of the *C. albicans* strains did not respond to the 4% and the 2% miconazole nitrate treatment regimens, respectively. These results suggest that the 7 day treatment arm may be superior in curing VVC infections due to *C. albicans*

strains. The exact reason for this difference in failure rates is unknown. It is possible that *C. albicans* strains with intermediate susceptibility to miconazole responded due to the longer duration of therapy while fully susceptible strains responded equally to both therapeutic regimens. To fully address this issue more patients would be required to enter the study and in vitro susceptibility testing would have to be performed on all fungal isolates.

The cure rate for *T. glabrata* infections was 1/7 (14.3%) and 1/5 (20%) in the 4% and the 2% miconazole treatment arms, respectively. This outcome demonstrates the inherent resistance of *T. glabrata* strains to antifungal azoles, including miconazole.

Lastly, it is of interest to note that the following species; *C. tropicalis, C. parapsilosis, Sac. cerevisiae, C. krusei* and *Monilia* sp. were seen in the failure group, the conversion group and the non-interpretable groups. However, miconazole in either formulation cured several vaginal infections due to *C. parapsilosis, C. krusei, C. lusitaniae* and *Candida* sp. The clinical significance of the cure and failure rates for these more resistant fungal strains cannot be accurately determined due to the small number of infections produced by these species in this study.

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1. Cotton, 1994. AIDS in Women. Textbook of AIDS Medicine. Williams and Wilkins. Chapter 11:161-168.D.

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10. Ferris, et. al., 1995. Office Laboratory Diagnosis of Vaginitis. J. Family Practice. 41:575-81.

11. Monif, 1985. Classification and pathogenesis of vulvovaginal candidiasis. Am. J. Obstet. Gynecol. 152:935.

12. Sobel, 1985. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. Am. J. Obstet. Gynecol. 152:924-35.

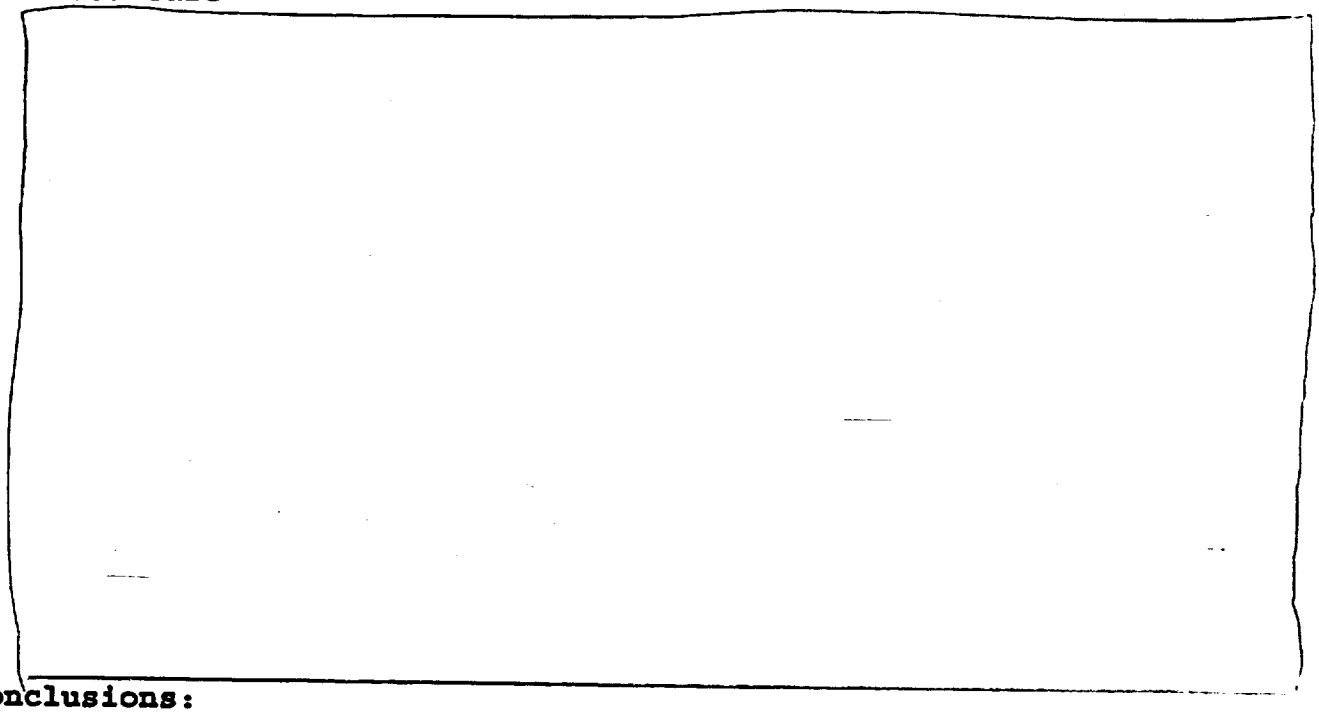
Recommended Future Studies:

This review of 4% miconazole nitrate cream points out several critical microbiologic issues that should be investigated in greater detail in future clinical trials. However, with respect to this product it is highly recommended that Advanced Care Products consider a phase IV study to determine if miconazole resistance developed in patients who failed 4% monistat therapy. Miconazole resistant fungal isolates should also be tested to determine the spectrum of cross resistance to other azole agents that would be used to treat VVC.

Labelling:

The approval of 4% miconazole nitrate cream is for over the counter use and must be in agreement with the Division of OTC Products guidelines. With respect to the proposed 4% miconazole nitrate label there are no microbiology issues. However, there are a number of issues that should be addressed in the class labeling of vaginal antifungal products. The OTC label for antifungal vaginal agents should be revised to include the information described below:

NDA 20827
Monistat 4% 3Day
Advanced Care



Conclusions:

Miconazole nitrate is an antifungal azole that is currently approved and marketed in a 2% cream formulation for the treatment of vaginal candidiasis (100 mg for 7 days). In this NDA the sponsor is proposing to double the concentration of miconazole to 4%, a 200 mg dose, which will be formulated in a new base cream. This new product will be administered intravaginally for 3 days.

In support of this NDA the sponsor submitted no new preclinical activity data, however, the clinical microbiologic data obtained from the clinical trials raised some concerns. First, in the two efficacy trials the overall microbiologic work-up of fungal cultures was adequate except for use the of BiGGY agar as the primary isolation medium for fungi. This growth medium has never been tested to determine if it can support the growth of clinically relevant fungal pathogens, specifically azole resistant *C. albicans* and *T. glabrata* species, which contribute to VVC in today's population. At this time nothing can be done with respect to the microbiologic data obtained from these clinical trials. However, it is highly recommended that in future clinical studies BiGGY agar not be used as the primary isolation medium for the recovery of yeasts until it can be further evaluated.

Second, the sponsor used the combined results of the KOH preparation and fungal culture to classify patients as a

microbiologic cure, failure or indeterminant. Several issues arose when the KOH and fungal culture results were discordant or one test result was missing. The protocol stipulated that if either test result was missing then that patient was categorized as indeterminate unless the other test result would have classified them as a failure. The classification of patients under this scenario is problematic for two reasons: a) fungal cultures are more specific and objective than KOH results which are largely subjective. As a consequence, fungal culture results should have been used as the definitive test for determining the microbiologic response; and b) the categorization of patients as a failure when only a positive KOH result was available or indeterminant if the KOH result was negative may have biased the results to produce higher failure rates in this study using the least sensitive microbiologic test. The use of the KOH preparation as a defining test for determining the microbiologic response in a clinical trial is inappropriate.

Third, when designing the clinical trial the sponsor made no provisions for differentiating colonization versus reinfection. This may explain why there were lower cure rates at RV2 versus RV1. Colonization of Candida in the vaginal tract is normal and occurs in approximately 15-20% of asymptomatic women. In this study women who were initially cured of VVC at RV1 then had a positive fungal culture or KOH at RV2 may have actually been microbiologically cured of their infection and only recolonized with yeast. However, these individuals were classified by the sponsor as a microbiologic failure.

In an effort to obtain a more definitive assessment of microbiologic outcome an independent assessment of the microbiologic data was conducted. In this analysis fungal culture results were used as the definitive microbiologic response.

The FDA's analysis of study 95-005 demonstrated equivalence with respect to microbiologic cure rates, 74% vs 74%, for subjects treated with 4% and 2% miconazole, respectively. However, in study 95-007 the overall microbiologic cure rates for patients receiving the 4% miconazole nitrate cream and the 2% miconazole cream as determined by the FDA were 64% and 75%, suggesting a higher microbiologic cure rate in control arm.

While the overall cure rates between the two treatment arms were comparable for the most part, the FDA analysis demonstrated that the majority of the failures were due to *C. albicans* and *T. glabrata* strains. When individual fungal

strains were evaluated it was noted that 15% and 10.6% of the *C. albicans* strains and 85.7% and 80% of the *T. glabrata* strains failed to respond to the 4% and the 2% miconazole nitrate treatment regimens, respectively. These results suggest that the 7 day treatment arm may be superior in curing VVC infections due to *C. albicans* strains. However, *T. glabrata* infections appear to be inherently resistance to either miconazole treatment regimen.

With respect to the other fungal species identified in the clinical trial an accurate assessment of the cure rates for these other Candida species could not be determined due to the small number of isolates recovered in these two studies. However, it should be noted that these isolates; *C. tropicalis, C. parapsilosis, C. lusitaniae, Sac. cerevisiae, C. krusei* and *Monilia* sp. appear to be inherently resistant to antifungal azoles and the majority were seen in the failure, conversion or non-interpretable categories. In studies 95-005 and 95-007 a small percentage of patients in both treatment arms (4% and 2% miconazole) had their fungal cultures convert from *C. albicans* to another fungal species. Again, it is of interest to note that the majority of the conversions were to more resistant strains of yeast.

With respect to the non-interpretable category, the predominate fungal strain seen in both treatment groups was *C albicans*. As the study was designed it is unknown whether these patients were just colonized or were actual relapses.

Finally, in reviewing this NDA submission several global issues arose regarding vaginal antifungal azole products. Historically, sponsors have not been asked to evaluate the rate of drug resistance development, the incidence of cross resistance or to determine potential adverse affects on special sub-populations of women receiving vaginal antifungal agents. However, the open literature now contains numerous articles that discuss how fungal populations are changing in women with VVC (i.e. more infections due to inherently resistant strains of fungi). A number of studies have observed that women with HIV, organ transplants or who are on chronic steroid or antibiotic therapy are at high risk for developing chronic VVC which is more severe and occurs more frequently requiring longer therapy. Data from other articles have shown that *Candida albicans* strains can develop cross resistance to antifungal azoles (i.e. ketoconazole and fluconazole) suggesting that cross resistance may potentially occur between the vaginal antifungal azoles.

At this time, it is unknown if drug resistance develops when recurrent VVC is treated with multiple doses of 4% miconazole, or if cross resistance occurs between miconazole and other vaginal antifungal azoles. To obtain this type of information future clinical trials should be designed to: 1) differentiate between colonization and relapse, 2) include routine susceptibility testing to determine if drug resistance has developed, 3) determine the incidence of cross resistance between vaginal antifungal agents.

Until better clinical trials can be performed to address these issues it is imperative that women purchasing this product and other similar products be informed of all potential benefits and adverse effects that may occur when using vaginal antifungal azoles.

In conclusion, this NDA is approved with respect to microbiology.

Recommendations:

There are no microbiology recommendations or comments to be conveyed to the sponsor at this time.

/S/

Linda L. Gosey
Microbiologist

Concurrences:

HFD-590/Dep Dir ___ /S/ _____Signature_____ Date
HFD-590/MicroTL____ _____ Signature 3/26/98 Date

CC:

HFD-590/ Orig.NDA:20-827
HFD-590/ Division File
HFD-590/MO:Davis
HFD-590/CSO:Chi
HFD-590/MicroTL:Lard
HFD-590/Chem
HFD-590/Pharm
HFD-590/Review Micro:Gosey
HFD-880/Bio-pharm:Colangelo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAR 10 1998

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**20-827**
Submission Dates:	March 31, 1997 (NDA) February 5, 1998 (Information Amendment)
Drug Product: **Trade Name:**	Miconazole Nitrate 4% Vaginal Cream MONISTAT®3
Sponsor:	Advanced Care Products New Brunswick, NJ
Category:	S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In:	April 21, 1997 (NDA) February 18, 1998 (Information Amendment)

I. BACKGROUND

Miconazole nitrate is a synthetic imidazole-derivative antifungal agent. The product, MONISTAT®, has been approved in several dosage forms for use in the U.S. and several other countries worldwide for the treatment of vulvovaginal candidiasis. MONISTAT® has been on the U.S. market for prescription use since 1974, and is currently available as a 2% (100 mg / 5 gm) vaginal cream, 100 and 200 mg vaginal suppositories, 100 mg tampon, and combination packs of suppositories (100 or 200 mg) and external vulvar cream for 3 to 7-day treatment of vulvovaginal candidiasis. The 2% cream and 100 mg vaginal suppositories have been approved from prescription to over-the-counter (OTC) use for 7-day treatment since 1991; the combination packs have been approved for 3 or 7-day OTC use since 1993.

In this current submission, the sponsor is seeking approval to market a higher strength 4% miconazole nitrate cream (200 mg / 5 gm) for direct OTC use as a 3-day treatment for vaginal candidiasis under the tradename MONISTAT®3 Vaginal Cream. It will be specifically indicated for the treatment of vulvovaginal candidiasis in women who have been previously diagnosed with vaginal yeast infections by their doctor and who recognize the same condition/symptoms again. The proposed dosage regimen is a single 200 mg dose (one full applicator) of the 4% cream intravaginally for 3 days. This regimen is identical to that of the currently marketed OTC MONISTAT®3 Combination Pack containing the 200 mg suppositories and external vulvar cream. The rationale for development of this newer product appeared to be driven by consumer preference, which according to the sponsor, was for a 3-day, cream-based treatment over the OTC products currently available (i.e., MONISTAT®7 Vaginal Cream or Suppositories; MONISTAT®3 or 7 Combination Packs). Thus, the 4% cream was developed using an improved base which is purported to retain viscosity at body temperature, and thereby reduce drip from the vagina.

II. SYNOPSIS

A copy of the proposed OTC labeling, including an educational brochure for the patient, is

provided with this review as **Appendix 1.**

Item 6: Human Pharmacokinetics and Bioavailability of this NDA submission contained one study (**Protocol 95-009-P**) to compare the absorption and systemic exposure to miconazole resulting from single and repeated intravaginal dose administration of the following three treatments:

(1) proposed 4% miconazole nitrate cream in the new more viscous base formulation, i.e., 200 mg x 3 days

(2) 2% miconazole nitrate cream in the same new more viscous base formulation, i.e., 100 mg MONISTAT®7 Vaginal Cream x 7 days

(3) 2% miconazole nitrate cream in the currently marketed less viscous base formulation, i.e., 100 mg MONISTAT®7 Vaginal Cream x 7 days

An application for market approval of the 2% cream in the new more viscous base formulation was submitted under NDA 17-450, Supplement SCF-043. Although this NDA was recently approved, this new cream has apparently not yet been marketed.

A more detailed review of **Protocol 95-009-P** can be found in **Appendix 2** (provided). Briefly, 42 healthy female volunteers were randomly assigned to the three treatment groups mentioned above (14 subjects / group). The pharmacokinetics of miconazole in plasma were determined after the initial (i.e., out to 24 hrs) and final (i.e., out to 24 and 72 hrs) intravaginal doses of study medications. Mean ± sd (range) PK parameters are provided below.

INITIAL INTRAVAGINAL DOSE

Treatment Group	Dose (mg)	N	AUC(0-24) (mcg.hr/L)	Cmax (mcg/L)	Tmax (hr)
MONISTAT®7 2% Marketed	100 x 1	14	32.1 ± 8.3 (15.5-42.7) [%RSD 26%]	1.99 ± 0.46 (1.01-2.66) [%RSD 23%]	12.3 ± 4.3 (8-24) [%RSD 35%]
MONISTAT®7 2% New Base	100 x 1	14	91.4 ± 35.3 (42.7-194.8) [%RSD 39%]	6.81 ± 2.36 (4.16-13.8) [%RSD 35%]	10.6 ± 2.0 (8-12) [%RSD 19%]
Miconazole 4% New Base	200 x 1	14	136.1 ± 45.7 (73.2-256.3) [%RSD 34%]	9.48 ± 2.92 (5.78-17.6) [%RSD 31%]	12.3 ± 2.9 (8-16) [%RSD 24%]

FINAL INTRAVAGINAL DOSE

Treatment Group	Dose (mg)	N	AUC(0-24) (mcg.hr/L)	AUC(0-72) (mcg.hr/L)	Cmax (mcg/L)	Tmax (hr)
MONISTAT®7 2% Marketed	100 x 7 Days	14	46.2 ± 12.8 (20.5-60.8) [%RSD 28%]	82.8 ± 28.4 (22.6-124.9) [%RSD 34%]	2.54 ± 0.58 (1.40-3.19) [%RSD 23%]	10.3 ± 3.0 (4-12) [%RSD 29%]
MONISTAT®7 2% New Base	100 x 7 Days	14	153.4 ± 64.4 (42.0-72.7) [%RSD 42%]	241.5 ± 118.2 (78.1-512.6) [%RSD 49%]	8.84 ± 2.95 (5.14-15.2) [%RSD 33%]	10.0 ± 2.1 (8-12) [%RSD 20%]

Miconazole 4% New Base	200 x 3 Days	14	215.8 ± 84.1 (103.3-423.9) [%RSD 39%]	365.6 ± 183.1 (148.8-838.4) [%RSD 50%]	12.68 ± 4.41 (6.63-23.1) [%RSD 35%]	12.6 ± 3.5 (8-16) [%RSD 28%]

Systemic absorption, and consequently, systemic exposure to miconazole following either initial or final (i.e., 7th) intravaginal dose of the 2% New Base formulation was ~3 to 4-fold higher when compared to the 2% Marketed product. Since the daily doses (100 mg) and total doses for the entire course of therapy (700 mg) were the same between the 2% New Base and 2% Marketed formulations, these results suggested an effect of the New Base on miconazole absorption from the vagina.

Compared to the MONISTAT®7 2% New Base cream, the magnitude of the increases in AUC and Cmax following either initial or final intravaginal doses of the miconazole nitrate 4% New Base cream formulation was less than proportional to the increase in the daily dose from 100 mg to 200 mg (i.e., 1.4 to 1.5-fold increases).

Compared to the MONISTAT®7 2% Marketed formulation, the magnitude of the increases in AUC and Cmax following either initial or final intravaginal doses of the miconazole nitrate 4% New Base cream formulation was more than proportional to the increase in daily dose from 100 mg to 200 mg (i.e., 4 to 5-fold increases). This would suggest an additional effect of the New Base on miconazole absorption from the vagina, besides the effect of the increase in daily dose.

Plasma miconazole concentrations were quantifiable [redacted] in nearly all subjects at predose (0 hrs) and at 72 hours after final dose administration of all three cream treatments. Mean plasma miconazole levels at 72 hrs after the final dose was the highest for the 4% New Base formulation at [redacted] followed by the 2% New Base cream at [redacted] then the 2% Marketed cream at [redacted]

Plasma accumulation of miconazole following final doses of the 2% (i.e., 100 mg x 7 days) and 4% (i.e., 200 mg x 3 days) New Base formulations appeared to be more extensive than that observed following the final dose of the 2% Marketed product (i.e., 100 mg x 7 days). For the MONISTAT®7 2% and miconazole nitrate 4% New Base formulations, plasma concentrations after the final doses were, on average, ~70% and ~60% higher, respectively, than miconazole levels after the initial doses. For the MONISTAT®7 2% Marketed product, plasma concentrations after the final dose were, on average, ~40% higher than those after the initial dose.

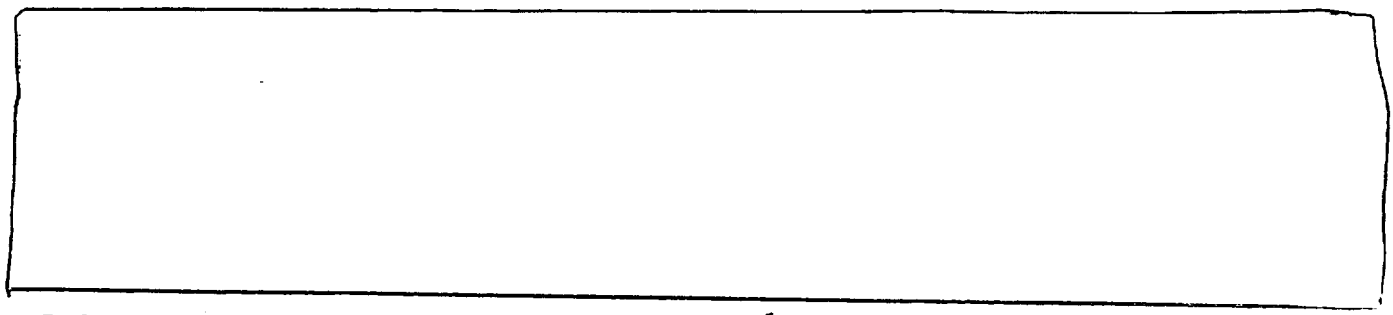
III. RECOMMENDATION

The information in Item 6 of NDA [redacted] for miconazole nitrate 4% 3-day vaginal cream has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and was found to be acceptable and adequate to support the approval of this product. There are no comments for the sponsor, and there are no labeling commments.

IV. GENERAL COMMENTS

[redacted]

2 ***pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.***



References:

(1) Daneshmend, TK and Warnock, DW. Clinical Pharmacokinetics of Systemic Antifungal Drugs, Clin Pharmacokinetics 8:17-42; 1983.

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(6) Maurice M, Pichard L, Daujat M, et.al. Effects of imidazole derivatives on cytochromes 450 from human hepatocytes in primary culture, FASEB J 6:752-758; 1992.

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(8) Pasanen M, Taskinen T, Iscan M, et. al. Inhibition of human hepatic and placental xenobiotic monooxygenases by imidazole antimycotics, Biochem Pharmacol 37:3861-3866; 1988.

(9) Back DJ, Tjia TF, et. al. In vitro inhibition studies of tolbutamide hydroxylase activity of human liver microsomes by azoles, sulphonamides, and quinolones, Br J Clin Pharmac 26:23-29; 1988.

/S/ 3/10/98

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D (Acting TL) /S/ 3/10/98
OCPB Briefing (3/5/98) Attendees: J. Lazor, F. Ajayi, J. Jenkins, B. Leissa, D. Davis, C. Chi

cc:
Div. File: NDA 20-287
HFD-590 (B. Leissa, TL, MO; D. Davis, MO)
HFD-590 (C. Chi, PM/CSO)
HFD-560 (L. Chin; L. Katz)
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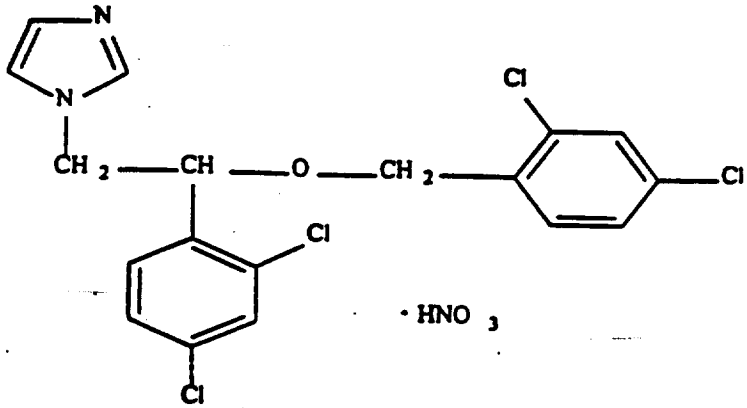
HFD-340 (Viswanathan)
HFD-205 (FOI)
HFD-880 (Division File)
HFD-880 (F. Ajayi; P. Colangelo)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

V. DRUG CHARACTERISTICS and FORMULATION

1. Chemistry

Miconazole nitrate is a synthetic imidazole-derivative antifungal which has the following chemical structure (MW 479.15):



2. Formulation

The miconazole 4% vaginal cream is formulated as a viscous oil and water emulsion into which the miconazole nitrate drug substance is suspended. This emulsion system is the same as that developed for the recently approved more viscous MONISTAT® 7 2% vaginal cream (NDA 17-450, SCF 043). A comparison of the original, currently marketed, less viscous MONISTAT® 7 2% vaginal cream (NDA 17-450), the recently approved more viscous MONISTAT® 7 2% vaginal cream, and the currently proposed more viscous 4% cream formulation [redacted] are provided at the end of this section as **Attachment 1.**

The sponsor indicated that the batches of the proposed 4% cream used in the two pivotal clinical efficacy trials, the pharmacokinetic study, and for stability testing were manufactured at full production scale [redacted] on the NDA-specified equipment at the NDA-specified manufacturing site [redacted] Thus, there appears to be no need to extrapolate clinical or stability data from smaller, non-production scale batches, different manufacturing equipment, or different manufacturing sites.

Stability evaluation of three batches [redacted] of the proposed NDA [redacted] included determinations of chemical stability of drug substance and preservative agent, viscosity, pH, particle size of drug substance, and *in vitro* release characteristics of the cream. A detailed review of these stability evaluations can be found in the Chemist's review of the NDA. It is important to note here in the OCPB review that, according to the sponsor, the *in vitro* release rate testing of the stability batches was performed only for the purpose of demonstrating lot-to-lot comparability. The sponsor further indicated that since there is a particle size specification established for the bulk drug substance, there was no crystal growth demonstrated in the formulation, and the emulsion was stable, release rate testing would not be routinely performed on the commercial product. Thus, there is no *in vitro* release rate specification for the finished product in the NDA. *This is consistent with current Agency guidelines on semi-solid dosage forms in that the development and validation of an in vitro release test are not required for approval of an NDA, nor is in vitro release required as a routine*

batch-to-batch quality control test. The procedures and results (i.e., Table XII) of the *in vitro* release tests of the three NDA stability batches are provided as **Attachment 2** at the end of this section. The results indicated similar release rates across the three stability batches.

ATTACHMENT 1:

MICONAZOLE NITRATE CREAM FORMULATION COMPARISONS

QUANTITATIVE NDA FORMULATIONS [% (w/w)]

Ingredient	MONISTAT® 7 2% Cream *less viscous, marketed* **NDA 17-450**	MONISTAT® 7 2% Cream *more viscous, approved* **NDA17-450 SCF-043**	**MONISTAT® 3 4% Cream *more viscous, proposed*** **[Formula No.] NDA 20-827**
Miconazole Nitrate, USP	2.00	2.000	**4.000**
Cetyl Alcohol, NF	-		
Stearyl Alcohol, NF	-		
Isopropyl Myristate, NF	-		
Propylene Glycol, USP	-		
Polysorbate 60, NF	-		
Purified Water, USP			
Benzoic Acid, USP			

3 pages of revised draft labeling have been redacted from this portion of the document.

Protocol 95-009-P - An Open Label Study of the Drug Absorption from Miconazole Nitrate 3-Day Vaginal Cream, MONISTAT®7 Vaginal Cream (New Base Formulation), and MONISTAT®7 Vaginal Cream (Marketed Formulation) in Normal Volunteers (Report No. 95-009-CR; Study Dates: 12/95 - 02/96)

Objective:
To evaluate the systemic absorption of miconazole from three cream formulations and to evaluate the safety/toleration of these formulations in healthy female volunteers.

Formulations/Treatments:
(i) **Miconazole Nitrate 2% Vaginal Cream (MONISTAT®7) - Marketed Formulation; less viscous;** approved and marketed for 7-day treatment of vulvovaginal candiasis; 100 mg miconazole nitrate per 5 gm cream dose

(ii) **Miconazole Nitrate 2% Vaginal Cream (MONISTAT®7) - New Base Formulation; more viscous;** approved but not yet marketed for 7-day treatment of vulvovaginal candiasis; 100 mg miconazole nitrate per 5 gm cream dose;

(iii) **Miconazole Nitrate 4% Vaginal Cream - New Base Formulation; more viscous;** proposed for 3-day treatment of vulvovaginal candiasis; 200 mg miconazole nitrate per 5 gm cream dose

Subjects:
42 healthy female subjects, randomly assigned to 3 treatment groups:

MONISTAT®7 - 2% Marketed Vaginal Cream Formulation
N = 14 (3 B*, 9 H*, 2 W*); mean age 33.6 yrs (range 20-45 yrs)

MONISTAT®7 - 2% New Base Vaginal Cream Formulation
N = 14 (1 B*, 9 H*, 4 W*); mean age 30.4 yrs (range 22-38 yrs)

Miconazole Nitrate 4% New Base Vaginal Cream Formulation
N = 14 (8 B*, 3 H*, 3 W*); mean age 33.7 yrs (range 22-44 yrs)

[* B = Black; H = Hispanic; W = White]

Design and Methods:
Randomized, open-label, parallel group design using the three treaments described above. Each of the 14 subjects assigned to the MONISTAT® 7 2% Marketed and New Base treatments received single daily 100 mg miconazole /5 gm cream doses intravaginally for 7 days for a total dose of 700 mg of each formulation. The 14 subjects assigned to the miconazole nitrate 4% New Base treatment received a single daily 200 mg miconazole /5 gm cream dose intravaginally for 3 days for a total dose of 600 mg. Blood samples for determination of plasma miconazole concentrations were collected at predose (0 hrs), 2, 4, 8, 12, 16, and 24 hrs after first dose administration, and at predose, 2, 4, 8, 12, 16, 24, 32, 48, and 72 hrs after final dose administration. Following intravaginal cream administration, subjects remained supine for 4 hrs and limited their physical activity for the duration of the study.

Analytical Methods:

Data Analysis:
The pharmacokinetic (PK) parameters, i.e., AUC(0-24), AUC(0-72), Cmax, and Tmax, were determined

after the first and final dose administrations using standard noncompartmental methods. The effect of changing the cream base on the systemic absorption of miconazole was examined at the same dose by comparing these parameters for the MONISTAT® 7 Marketed and New Base formulations. The effect of doubling the dose in the New Base formulation was also compared by evaluating the PK parameters for the miconazole 2% and 4% creams. In addition, the systemic absorption and accumulation of miconazole in plasma was also assessed after multiple dose administration of the 3-day and 7-day regimens. Safety and/or toleration was assessed through evaluation of adverse experiences, vital signs, routine laborartory tests, and gynecological examinations.

Results:

Initial/Single Dose PK

Figure 1 illustrates the mean plasma miconazole concentration-time profiles for the 3 treatments after initial dose administration. Mean miconazole plasma concentrations were higher at all timepoints after administration of the MONISTAT®7 New Base compared to the MONISTAT®7 Marketed formulation. Mean plasma concentrations after the 4% New Base cream were higher than those for the MONISTAT®7 2% New Base cream, but the increase was generally less than proportional to the increase in dose. Increases in mean plasma concentrations were substantially greater than the increase in dose (i.e., 4 to 5-fold) at all timepoints for the 4% New Base cream compared to the MONISTAT®7 2% Marketed formulation.

The individual concentration and PK data are provided in Table 1. Predose concentrations were below the lower limit of quantitation [redacted] for all treatment groups. For the MONISTAT®7 Marketed formulation group, 8 of 14 subjects had miconazole levels that were also LLOQ at 2 hrs postdose, compared to 2 of 14 subjects in the MONISTAT® 7 New Base and 3 of 14 subjects in the Miconazole Nitrate 4% 3-Day New Base formulation groups. The table below summarizes the mean PK parameters following single dose administration of the 3 cream formulations:

Mean ± SD (Range) Pharmacokinetic Parameters for Miconazole After Initial Intravaginal Dose Administration

Treatment Group	Dose (mg)	N	AUC(0-24) (mcg.hr/L)	Cmax (mcg/L)	Tmax (hr)
MONISTAT®7 2% Marketed	100 x 1	14	32.1 ± 8.3 (15.5-42.7) [%RSD 26%]	1.99 ± 0.46 (1.01-2.66) [%RSD 23%]	12.3 ± 4.3 (8-24) [%RSD 35%]
MONISTAT®7 2% New Base	100 x 1	14	91.4 ± 35.3 (42.7-194.8) [%RSD 39%]	6.81 ± 2.36 (4.16-13.8) [%RSD 35%]	10.6 ± 2.0 (8-12) [%RSD 19%]
Miconazole 4% New Base	200 x 1	14	136.1 ± 45.7 (73.2-256.3) [%RSD 34%]	9.48 ± 2.92 (5.78-17.6) [%RSD 31%]	12.3 ± 2.9 (8-16) [%RSD 24%]

The mean AUC(0-24) and Cmax estimates for the 100 mg dose of the MONISTAT®7 2% New Base cream were 2.8- and 3.4-fold higher, respectively, than the mean estimates for the same dose of the MONISTAT®7 2% Marketed formulation. The mean AUC(0-24) and Cmax values following the 200 mg dose of the Miconazole 4% New Base cream were 1.5- and 1.4-fold higher, respectively, than the same estimates obtained after the 100 mg dose of the MONISTAT®7 2% New Base formulation, indicating less than dose proportional increases in systemic exposure to miconazole with the New Base. The mean AUC(0-24) and Cmax estimates following the 200 mg dose of the Miconazole 4% New Base cream were 4.2- and 4.8-fold higher, respectively, than the same estimates obtained after the 100 mg dose of the MONISTAT®7 2% Marketed formulation, indicating substantially greater than dose proportional increases in systemic exposure to miconazole with the New Base compared to the Marketed formulation. Mean

Tmax values for all 3 formulations were similar, ranging from ~11 to 12 hrs.

Final/Multiple Dose PK

Figure 2 illustrates the mean plasma miconazole concentration-time profiles following the final intravaginal doses. The individual concentration and PK data are provided in Table 2. Miconazole plasma concentrations at predose were quantifiable [redacted] for all subjects in all 3 treatment groups. At 72 hrs postdose, plasma miconazole levels remained quantifiable [redacted] for all 14 subjects in the 4% New Base group, in 13 of 14 subjects in the MONISTAT®7 2% New Base group, and in 12 of 14 subjects in the MONISTAT®7 2% Marketed formulation group. The mean concentration profiles following the final doses showed a similar pattern to that after initial dose administration, with less than dose proportional increases between the 4% (200 mg) and 2% (100 mg) New Base formulations, and substantially greater than dose proportional increases (i.e., 3- to 5-fold) between the 4% (200 mg) New Base cream and the 2% (100 mg) Marketed product.

The table below summarizes the mean PK parameters following final dose administration of the 3 cream formulations:

Mean ± SD (Range) Pharmacokinetic Parameters for Miconazole After Final Intravaginal Dose Administration

Treatment Group	Dose (mg)	N	AUC(0-24) (mcg.hr/L)	AUC(0-72) (mcg.hr/L)	Cmax (mcg/L)	Tmax (hr)
MONISTAT®7 2% Marketed	100 x 7 Days	14	46.2 ± 12.8 (20.5-60.8) [%RSD 28%]	82.8 ± 28.4 (22.6-124.9) [%RSD 34%]	2.54 ± 0.58 (1.40-3.19) [%RSD 23%]	10.3 ± 3.0 (4-12) [%RSD 29%]
MONISTAT®7 2% New Base	100 x 7 Days	14	153.4 ± 64.4 (42.0-72.7) [%RSD 42%]	241.5 ± 118.2 (78.1-512.6) [%RSD 49%]	8.84 ± 2.95 (5.14-15.2) [%RSD 33%]	10.0 ± 2.1 (8-12) [%RSD 20%]
Miconazole 4% New Base	200 x 3 Days	14	215.8 ± 84.1 (103.3-423.9) [%RSD 39%]	365.6 ± 183.1 (148.8-838.4) [%RSD 50%]	12.68 ± 4.41 (6.63-23.1) [%RSD 35%]	12.6 ± 3.5 (8-16) [%RSD 28%]

Similar patterns of systemic exposure to miconazole were observed after multiple dose as with following initial dose administration. The mean AUC (both (0-24) and (0-72)) and Cmax estimates for the 100 mg dose of the MONISTAT®7 2% New Base cream were ~3 and 3.5-fold higher, respectively, than the mean estimates for the same dose of the MONISTAT®7 2% Marketed formulation. The mean AUC (both (0-24) and (0-72)) and Cmax values following the 200 mg dose of the Miconazole 4% New Base cream were 1.4- to 1.5-fold higher than the same estimates obtained after the 100 mg dose of the MONISTAT®7 2% New Base formulation, indicating less than dose proportional increases in systemic exposure to miconazole with the New Base. The mean AUC (both (0-24) and (0-72)) and Cmax estimates following the 200 mg dose of the Miconazole 4% New Base cream were ~4.5- and ~5-fold higher, respectively, than the same estimates obtained after the 100 mg dose of the MONISTAT®7 2% Marketed formulation, indicating substantially greater than dose proportional increases in systemic exposure to miconazole with the New Base compared to the Marketed formulation. Mean Tmax for the 4% New Base cream was prolonged by ~2 hrs at 12.6 hrs. compared to ~10 hrs for the MONISTAT®7 2% New Base and Marketed formulations.

Plasma accumulation of miconazole, as evaluated by the ratio of mean AUC(0-24) after the final dose to the mean AUC(0-24) after the initial dose, appeared to be more extensive for both of the New Base formulations compared to the Marketed formulation. For the MONISTAT®7 2% and miconazole nitrate 4% New Base formulations, plasma concentrations after the final doses were, on average, ~70% and ~60% higher, respectively, than miconazole levels after the initial doses (i.e., mean $AUC(0\text{-}24)_{final}$/mean $AUC(0\text{-}24)_{initial}$ = 1.68 for 2%; 1.59 for 4%). For the MONISTAT®7 2% Marketed product, plasma

concentrations after the final dose were, on average, ~40% higher than those after the initial dose (i.e., mean $AUC(0\text{-}24)_{final}$/mean $AUC(0\text{-}24)_{initial}$ = 1.44).

Total variability in the AUC and Cmax estimates (i.e, as %RSD) was slightly higher for both of the New Base formulations following the initial and final doses when compared to the Marketed formulation at 31-50% vs. 23-34%.

In general, there were no significant adverse events observed or other safety/toleration issues noted to warrant any subject to discontinue from the study. Abdominal cramping, headache, and urticaria appeared to be the most frequent adverse events reported, with all 3 formulations having similar occurrence rates. Post-study (i.e., follow-up) gynecologic examinations revealed two subjects with external erythema in the vulvar area. The first subject was receiving the 4% New Base formulation and the second was receiving the 2% Marketed product. In the case of the second subject, this was noted as not likely to be related to study drug administration, while nothing was noted with respect to relationship to study drug for the first subject. Another noteworthy gynecologic finding reported on the subjects' case report forms was the observance of slight, moderate, or heavy leakage from the vagina after cream administration during the study. Slight leakage was reported in 6 of 14 subjects for the 4% (3-Day) New Base cream; slight, moderate, and/or heavy leakage was reported in 8 of 14 subjects for the 2% (7-Day) New Base cream and in 11 of 14 subjects for the 2% (7-Day) Marketed cream.

Conclusions:

The PK data indicated:

Systemic absorption, and consequently, systemic exposure to miconazole following either initial (i.e., after the 1st dose) or final (i.e., after the 7th dose) intravaginal administration of the 2% New Base formulation (MONISTAT®7) was ~3 to 4-fold higher when compared to the 2% Marketed MONISTAT®7 product. Since the daily doses (100 mg) and total doses for the entire course of therapy (700 mg) were the same between the 2% New Base and 2% Marketed formulations, these results would suggest an effect of the New Base on miconazole absorption from the vagina;

Compared to the MONISTAT®7 2% New Base cream, the magnitude of the increases in AUC and Cmax following either initial or final intravaginal doses of the miconazole nitrate 4% New Base cream formulation was less than proportional to the increase in dose from 100 mg to 200 mg (i.e., 1.4 to 1.5-fold increases);

Compared to the MONISTAT®7 2% Marketed formulation, the magnitude of the increases in AUC and Cmax following either initial or final intravaginal doses of the miconazole nitrate 4% New Base cream formulation was more than proportional to the increase in dose from 100 mg to 200 mg (i.e., 4 to 5-fold increases). This would suggest an additional effect of the New Base on miconazole absorption from the vagina, besides the effect of the increase in dose;

Plasma miconazole concentrations were quantifiable [redacted] in nearly all subjects at predose and at 72 hours after final dose administration of all three cream treatments;

Plasma accumulation of miconazole following final doses of the 2% (i.e., 7 days) and 4% (i.e., 3 days) New Base formulation appeared to be more extensive than that observed following the final dose of the 2% Marketed product (i.e., 7 days). For the MONISTAT®7 2% and miconazole nitrate 4% New Base formulations, plasma concentrations after the final doses were, on average, ~70% and ~60% higher, respectively, than miconazole levels after the initial doses. For the MONISTAT®7 2% Marketed product, plasma concentrations after the final dose were, on average, ~40% higher than those after the initial dose;

The incidence of adverse effects appeared to be similar across all three treatments. However, the occurrence and extent of leakage of cream from the vagina appeared to be greatest for the MONISTAT®7 Marketed product (i.e., 11 of 14 subjects; ~79%), followed by the MONISTAT®7 New Base formulation

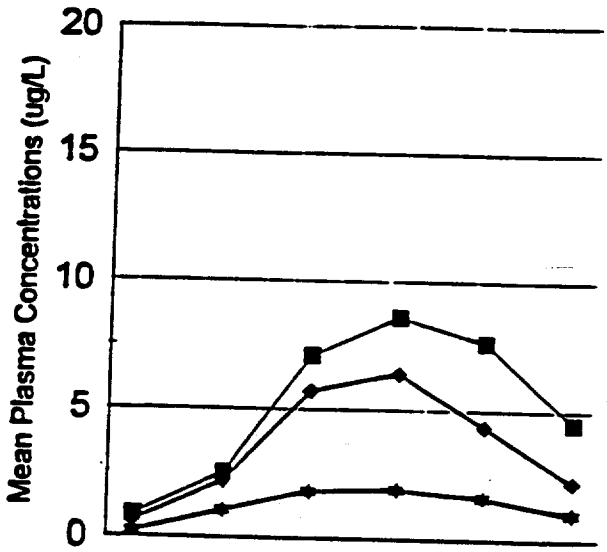
(i.e., 8 of 14 subjects; ~57%), and the least with the miconazole nitrate 4% New Base formulation (i.e., 6 of 14 subjects; ~43%).

Comments:
See Section IV. General Comments (Not to be Sent to Sponsor) above.

APPEARS THIS WAY
ON ORIGINAL

FIGURE # 1

MEAN PLASMA CONCENTRATIONS OF MICONAZOLE (ug/L)
FOLLOWING INITIAL DOSE ADMINISTRATION

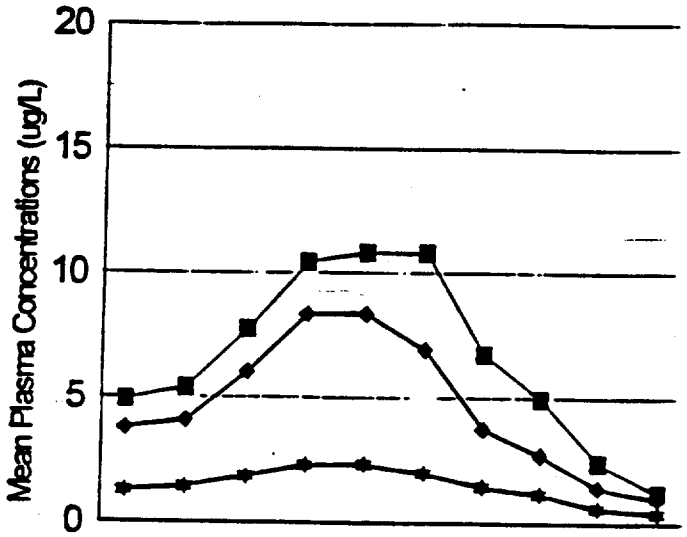


Hours	2	4	8	12	16	24
miconazole 3-day	0.876	2.501	7.102	8.619	7.644	4.510
M-7 New	0.616	2.166	5.714	6.410	4.381	2.230
M-7 Marketed	0.207	1.029	1.796	1.904	1.621	1.016

FIGURE # 2

MEAN PLASMA CONCENTRATIONS OF MICONAZOLE (ug/L)

FOLLOWING FINAL DOSE ADMINISTRATION



Hours	0	2	4	8	12	16	24	32	48	72
miconazole 3-day ■	4.916	5.390	7.745	10.438	10.820	10.811	6.751	4.956	2.435	1.220
M-7 New ◆	3.764	4.056	6.011	8.349	8.366	6.936	3.758	2.730	1.440	0.979
M-7 Marketed ✱	1.273	1.434	1.859	2.313	2.346	2.001	1.466	1.179	0.606	0.404

4 ***pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.***