

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020968**

**MICROBIOLOGY REVIEW(S)**

HFD 590/C.Chi

JAN 29 1999

JGU

REVIEW FOR HFD-590  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGIST'S REVIEW #1 OF NDA

January 21, 1999

A. 1. NDA 20-968

SPONSOR Advanced Care Products  
199 Grandview Road  
Skillman, New Jersey 08558-9418

2. PRODUCT NAMES: Miconazole Nitrate, USP; MONISTAT®

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Vaginal

4. METHOD(S) OF STERILIZATION

5. PHARMACOLOGICAL CATEGORY: Anti-Fungal

6. DRUG PRIORITY CLASSIFICATION:

B. 1. DATE OF INITIAL SUBMISSION: June 30, 1998

2. DATE OF AMENDMENT: N/A

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: January 15, 1999

C. REMARKS: This review addresses the Microbial Limit specifications and procedures for the drug product.

D. CONCLUSIONS: This submission is recommended for approval.

/S/  
Bryan Riley, Ph.D.

1-21-99

/S/

1/29/99

cc:

- HFD 590/Consult File
- HFD 590/C. Chi
- HFD 590/D. Matecka
- HFD 805/Consult File
- HFD 805/B. Riley

Drafted by: B. Riley, 1/21/99  
R/D initialed by: P. Cooney,

APPEARS THIS WAY  
ON ORIGINAL



NDA 20-968

Monistat 1 (1200 mg/ [redacted] and external cream  
Advanced Care Products

**Background:**

In NDA #20-968 the sponsor has requested approval of miconazole nitrate (1200 mg) in a solid vaginal [redacted] with 2% miconazole nitrate external cream as a 1 day treatment regimen for vaginal candidiasis. This application is for prescription use only. The microbiology review of the preclinical and clinical data can be found in document NDA 20968.0. This supplement contains the sponsor's updated label incorporating the FDA's recommendations.

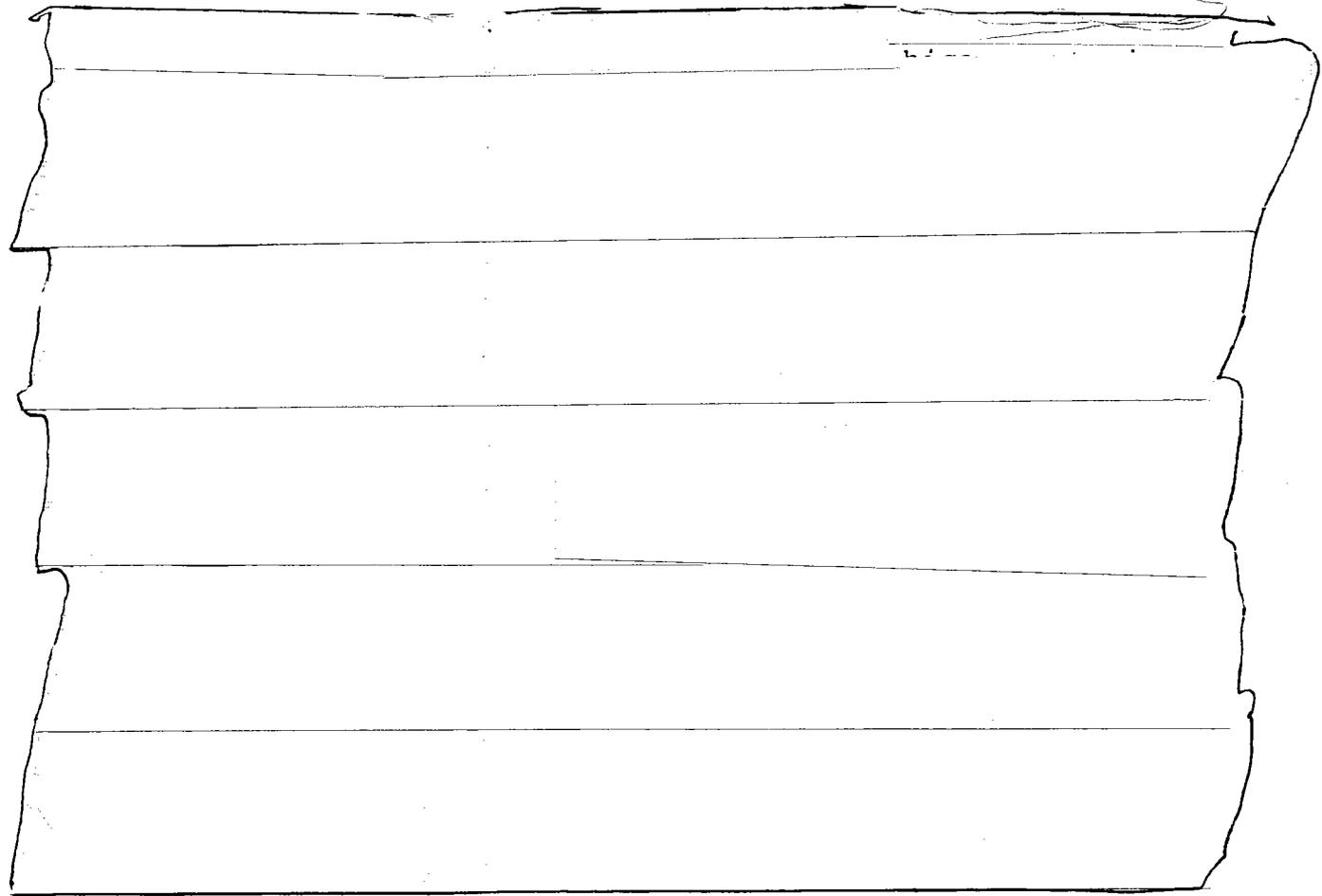
**Sponsor's proposed Label:**

**CLINICAL PHARMACOLOGY**

This section is redacted with a hand-drawn border and contains several horizontal lines, indicating that the content has been obscured.

NDA 20-968

Monistat 1 (1200 mg  ) and external cream  
Advanced Care Products



**Conclusions:**

The FDA is in agreement with the sponsor's proposed wording of the microbiology section of the Monistat Dual-Pak label except for one typographical error. In the susceptibility testing section, first paragraph, the fourth sentence should read "Most strains of *Candida albicans* exhibited miconazole MICs of  $\leq 0.01$  ug/mL (#1)."

In a telecon held on June 25, 1999 the Division and sponsor agreed upon the wording change in the microbiology section of the "Monistat Dual-Pak" label. The sponsor committed in writing that they would make this change to the final draft label. Therefore, the reviewing microbiologist recommends approval of NDA 20-968.

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Monistat 1 (1200 mg [redacted]) and external cream  
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**Recommendations:**

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

[redacted signature]

Linda L. Gosey  
Microbiologist (HFD 590)

APPEARS THIS WAY  
ON ORIGINAL

**Concurrences:**

HFD-590/Dep Dir [redacted]  
HFD-590/Micro TL [redacted]

Signature 7/15/99 Date  
Signature 7/13/99 Date

**CC:**

- HFD-590/ Orig.NDA#20-968
- HFD-590/ Division File
- HFD-590/MO
- HFD-590/CSO
- HFD-590/Chem
- HFD-590/Pharm
- HFD-590/Review Micro:Gosey

APPEARS THIS WAY  
ON ORIGINAL

JUN 28 1999

Microbiology Review

Division of Special Pathogens and Immunologic Drug Products

(HFD-590)

NDA# 20-968

Reviewer : Linda Gosey  
Correspondence Date : 5-07-99  
CDER Receipt Date : 5-11-99  
Review Assigned Date: 5-21-99  
Review Complete Date: 6-25-99

Sponsor: Advanced Care Products  
691 Highway 1 South  
PO Box 6024  
North Brunswick, New Jersey 08902

Submission Reviewed: Supplement BL

Drug Category: Vaginal antifungal

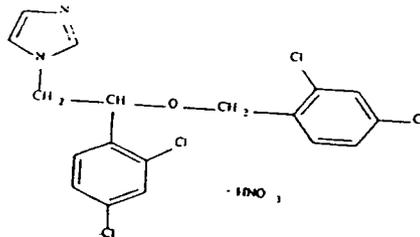
Indication: Treatment of vulvovaginal candidiasis

Dosage Form: Soft gel vaginal insert/external cream

Product Names:

- a. Proprietary: Monistat Dual-Pak
- b. Nonproprietary: Miconazole nitrate (1200 mg vaginal )  
with 2% miconazole nitrate cream (external use)
- c. Chemical: 1-[2,4-dichloro-B-[(2,4-dichlorobenzyl)oxyl]  
phenethyl] imidazole nitrate

Structural Formula:



Supporting Documents: DMF  
DMF

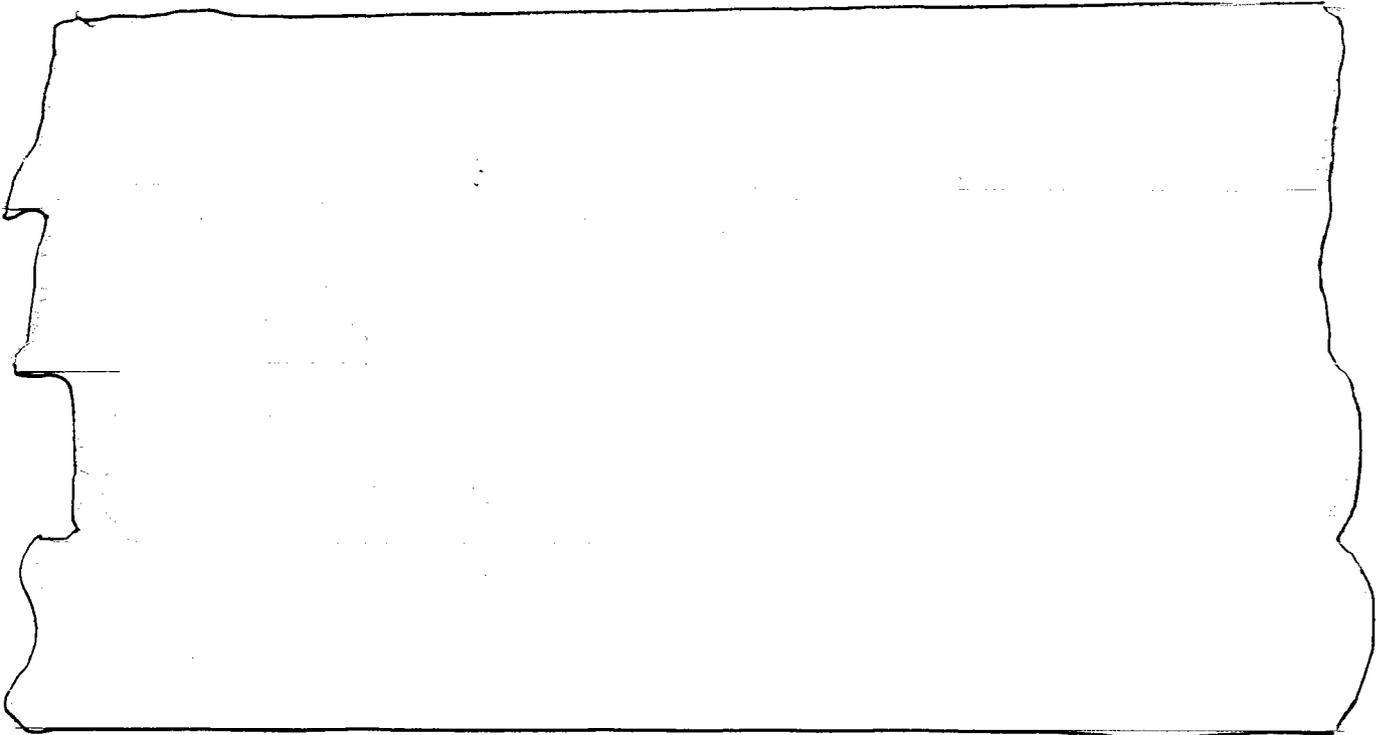
NDA 20-968

Monistat 1 (1200 mg [redacted] and external cream  
Advanced Care Products

**Background:**

In NDA #20-968 the sponsor has requested approval of miconazole nitrate (1200 mg) in a solid vaginal [redacted] with 2% miconazole nitrate external cream as a 1 day treatment regimen for vaginal candidiasis. This application is for prescription use only. The microbiology review of the preclinical and clinical data can be found in document NDA 20968.0. This supplement contains the sponsor's proposed label.

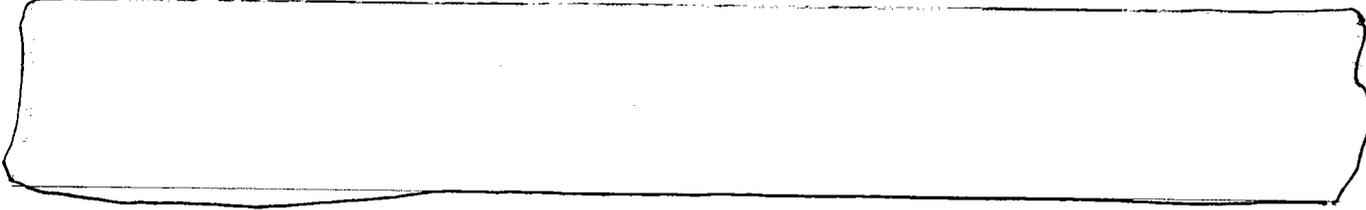
**Labeling:**



FDA's proposed microbiology section of the 1200 mg miconazole nitrate ovule label:

**CLINICAL PHARMACOLOGY**

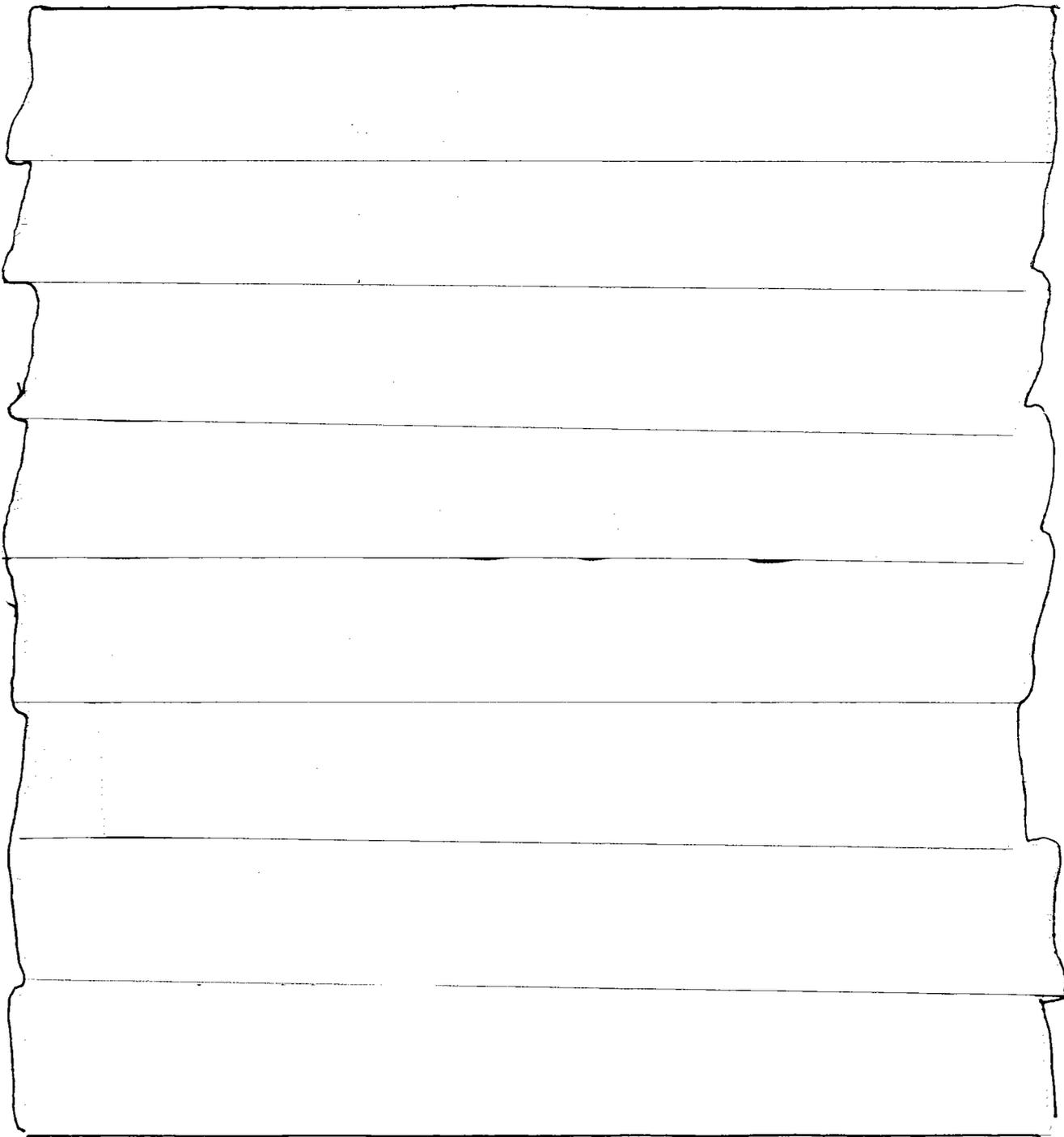
**Microbiology:**



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Monistat 1 (1200 mg \_\_\_\_\_ and external cream

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NDA 20-968

Monistat 1  and external cream

Advanced Care Products


**Conclusions:**

Miconazole nitrate is an antifungal azole that is currently approved and marketed in several formulations for the treatment of vulvovaginal candidiasis. In this NDA the sponsor has proposed to incorporate 1200 mg miconazole nitrate into an ovule that will be administered intravaginally as a single dose. This product will be marketed by prescription use only.

Antifungal azoles, as a drug class, have characteristic activity and resistance properties. Published articles have reported that drug resistant strains of *Candida albicans* have emerged when antifungal azole therapy is used chronically over long periods of time. In addition, cross resistance between antifungal azoles has been observed with various *Candida* species. Yeast strains such as *C. krusei*, *C. glabrata*, *C. parapsilosis* are generally inherently resistant to antifungal azoles. As a result, the reviewing microbiologist recommends

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Monistat 1 (1200 mg [redacted] and external cream  
Advanced Care Products

that this information be incorporated into all prescription vaginal azole products.

With respect to miconazole nitrate, preclinical activity data have demonstrated that this drug has some activity against most *Candida* species. Trends in data from clinical trials evaluating miconazole nitrate cream formulas suggest that there is an increased incidence, though not statistically significant at this time, of inherently resistant strains of *Candida* in patients who relapse or fail therapy. An indepth evaluation of the 1200 mg miconazole [redacted] in the clinical trials submitted in this NDA was not possible given the fungal pathogens were not speciated and antifungal susceptibility testing was not conducted.

There is a sufficient body of data available describing the resistance and cross resistance patterns of antifungal azoles as a drug class. While reported clinical cases are rare, several published articles have described similar activity with pathogenic yeasts responsible for producing vulvovaginal candidiasis and miconazole nitrate treatment. In addition, *Candida* species demonstrating cross resistance between miconazole and two other antifungal azoles, econazole and clotrimazole, has been reported. As a result, the prescription label for the 1200 mg miconazole nitrate [redacted] should reflect these observations to assist the physician in the proper treatment of patients with vulvovaginal candidiasis.

On June 25, 1999 the Division and sponsor agreed upon the wording for the microbiology section of the "Monistat Dual-Pak" label contained within this review. Therefore, this NDA is approved with respect to microbiology.

**Recommendations:**

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

[redacted signature]

Linda L. Gosey  
Microbiologist (HFD 590)

NDA 20-968  
Monistat 1 (1200 mg ovule) and external cream  
Advanced Care Products

Concurrences:

HFD-590/Dep Dir

HFD-590/Micro TL

CC:

HFD-590/ Orig.NDA#20-968

HFD-590/ Division File

HFD-590/MO

HFD-590/CSO

HFD-590/Chem

HFD-590/Pharm

HFD-590/Review Micro:Gosey

/S/

/S/

Signature 6/28/99 Date

Signature 6/25/99 Date

APPEARS THIS WAY  
ON ORIGINAL

JUN 28 1999

Microbiology Review

Division of Special Pathogens and Immunologic Drug Products

(HFD-590)

NDA# 20-968

Reviewer : Linda Gosey  
Correspondence Date : 6-30-98  
CDER Receipt Date : 7-02-98  
Review Assigned Date: 7-15-98  
Review Complete Date: 4-05-99

Sponsor: Advanced Care Products  
691 Highway 1 South  
PO Box 6024  
North Brunswick, New Jersey 08902

Submission Reviewed: Original (date 6-30-98)

Drug Category: Vaginal antifungal

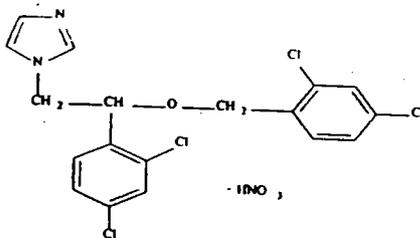
Indication: Treatment of vulvovaginal candidiasis

Dosage Form: Soft gel vaginal insert/external cream

Product Names:

- a. Proprietary: Monistat Dual-Pak
- b. Nonproprietary: Miconazole nitrate (1200 mg vaginal [redacted]  
with 2% miconazole nitrate cream (external use))
- c. Chemical: 1-[2,4-dichloro-B-[(2,4,-dichlorobenzyl)oxyl]  
phenethyl] imidazole nitrate

Structural Formula:



Supporting Documents: DMF [redacted]  
DMF [redacted]

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Monistat 1 (1200 mg [redacted]) and external cream  
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**Background:**

**Drug: 1200 mg Miconazole Nitrate [redacted]**

Miconazole nitrate was first approved in 1974 as a vaginal cream (2%, 100 mg) to be dosed daily for 14 days for the treatment of vaginal candidiasis. This treatment regimen was later reduced to 7 days. In March 1998 a 3 day treatment regimen with 4%, 200 mg miconazole nitrate cream was approved. The FDA has also approved miconazole nitrate formulated as a vaginal suppository (100 and 200 mg) and a 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 1 day treatment regimen with a 1200 mg miconazole nitrate [redacted] in combination with the use of the 2% external vulvar cream was compared to the 7 day treatment regimen (100 mg/day, 2% cream). Currently, the 1200 mg [redacted] 1 day treatment, is approved in 19 foreign countries.

The miconazole nitrate ovule is a solid dosage form where the parent drug is formulated in liquid paraffin, white petrolatum gelatin and lecithin. [redacted]

**Disease: Vulvovaginal Candidiasis:**

The intended use of this prescription 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 require 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

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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/mm<sup>3</sup> (#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 as well as chronic VVC.

**Summary:**

**Preclinical Microbiology Review:**

In this NDA the sponsor is seeking approval of miconazole nitrate (1200 mg) in a solid vaginal [redacted] with 2% miconazole nitrate external cream as a 1 day treatment regimen for vaginal candidiasis. In the preclinical microbiology section of the document the sponsor has submitted copies of in vitro or in vivo articles that have previously been used to demonstrate the antifungal activity of miconazole against *Candida* species.

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Because miconazole is already approved for the treatment of vaginal candidiasis it was not necessary to conduct a formal microbiology review of the submitted preclinical activity data.

#### Clinical Studies:

The approval of this new drug product required the demonstration of efficacy equivalence and bioequivalence between the proposed 1200 mg miconazole nitrate [redacted] single treatment with 2% miconazole nitrate external cream and the 7 day treatment course with 200 mg miconazole nitrate cream. To demonstrate equivalence the sponsor conducted a single pharmacokinetic study and two clinical efficacy trials.

The ovule used in the phase III clinical trial 96-002-P was manufactured at [redacted]. However, the ovule used in the 97-006-P phase III efficacy trial and the 97-007-P absorption study were manufactured at [redacted].

#### Protocol 97-007-P: Pharmacokinetic Study

In study 97-007 the absorption and pharmacokinetic characteristics of the 1200 mg miconazole nitrate [redacted] was assessed in normal female volunteers. In one cohort a single dose was administered, simulating the proposed actual use of the product. In a second cohort two doses were administered, 48 hours apart, to determine the effects in the event a subject accidentally overdosed themselves.

In the first cohort miconazole levels were determined in the serum at 0, 2, 4, 8, 12, 16, 24, 48, 72 and 96 hours following the administration of study drug. In cohort two serum drug levels were measured at 0, 2, 4, 8, 12, 16, 24, and 36 hours after the first dose and 2, 4, 8, 12, 16, 24, 48, 72 and 96 hours after the second dose. These test results will be reviewed by the Division's pharmacologist and the biopharmacology reviewer. However, there is a concern that the systemic levels of miconazole that result after vaginal dosing may be at or near the minimal inhibitory concentrations (MICs) for the Candida species which potentially could 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 Candida species. The majority of susceptible Candida species have a miconazole MIC of 0.01

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ug/mL. In the single dose pharmacokinetic study  $C_{max}$  levels were obtained approximately 18 hours post dosing. Serum concentrations of 9.2 - 10.1 ng/mL, which equals 0.0092 - 0.01 ug/mL, were achieved between 12 and 24 hours post drug dosing (See table 1). In the double dose study serum drug concentrations at or near the MIC were obtained 16 to 24 hours after the first dose and 8-24 hours after the second dose (See table 2 and 3).

Table 1

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Table I  
Dose Group 1: Mean Plasma Concentrations of Miconazole (ng/mL)

Treatment Group	Study Statistic	Pre Dose	Hours Post Study Drug Dose								
			2	4	8	12	16	24	48	72	96 <sup>b</sup>
Miconazole Nitrate (1200 mg) Vaginal One Dose N=10	Mean	*	a	1.223	6.638	9.214	10.072	9.220	4.512	2.954	1.840
	STD		-	0.779	2.181	2.702	3.301	3.714	2.732	2.704	1.947

Cross Reference: TABLE 2, page 35

\* All pre-dose values were below limit of quantitation.

a Was not calculated because 9 of 10 subjects had values below the level of quantification.

b Based on N=9.

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Table 2

Table II  
Dose Group 2 (Day 1): Mean Plasma Concentrations of Miconazole (ng/mL)

Treatment Group	Study Statistic	Pre Dose	Hours Post Initial Study Drug Dose (Day 1)							
			2	4	8	12	16	24	36	48+
Miconazole Nitrate (1200 mg) Vaginal Two Doses N=10	Mean	*	1.083a	1.486	7.798	8.873	9.414	9.041	6.936	6.075
	STD		-	0.825	2.508	2.303	1.884	2.938	4.142	5.173

Cross Reference: TABLE 2, page 37.

\* All pre-dose values were below limit of quantitation or missing.

+ Corresponds to Day 3 predose.

a Mean was calculated on 2 subjects. 8 subjects had values below the limit of quantification.

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 Monistat 1 (1200 mg [redacted] and external cream  
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Table 3

**Table III**  
**Dose Group 2 (Day 3): Mean Plasma Concentrations of Miconazole (ng/mL)**

		Hours Post Final Study Drug Dose (Day 3)									
Treatment Group	Study Statistic	+Pre Dose	2	4	8	12	16	24	48	72	96
Miconazole Nitrate (1200 mg) Vaginal Two Doses N=10	Mean	6.075	4.673	6.263	10.282	10.979	10.703	9.555	6.000	3.730	3.252
	STD	5.173	4.220	4.401	5.124	5.082	6.053	5.196	8.048	5.918	5.110
Cross Reference: TABLE 2, page 38.											

+ Corresponds to 48-hours post initial dosing.

**Comment:**

There is a concern regarding the systemic level of miconazole that is obtained when patients use this product to treat a vaginal infection. The PK/PD data show that after a single 1200 mg miconazole nitrate [redacted] is administered vaginally miconazole Cmax levels of approximately 0.01 ug/mL are achieved in the blood 12-24 hours post treatment. This systemic level of miconazole is comparable to miconazole MIC<sub>50</sub>s for *C. albicans* species ( $\leq 0.01$  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 ( $\leq 4$  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)). If this agent were to be used chronically in an immunocompromised patient population then sustained inhibitory levels would be achieved systemically potentially predisposing subjects to more severe fungal infections. Not only may prolonged use of this agent potentially create miconazole resistant *Candida albicans* strains but more serious infections due to naturally resistant strains of fungi (i.e. *C. glabrata*,

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*C. krusei*, *C. parapsilosis* and *C. tropicalis*) may also occur. In either case, the treatment of infections due to azole resistant fungal strains would be extremely difficult. This is an important issue in immunosuppressed subjects who are at risk for developing chronic oropharyngeal candidiasis and life-threatening fungal infections.

Protocols 96-002-P and 97-006-P: Efficacy studies

The design of the two efficacy trials were similar. Both studies were single-blind, randomized, multi-center, controlled, parallel group, comparative phase III trials in female patients with documented vulvovaginal candidiasis. Clinical trials 96-002-P and 97-006-P were conducted to compare the safety and efficacy of a single dose, 1200 mg miconazole nitrate vaginal ovule with 2% miconazole nitrate external cream to the approved 2% miconazole nitrate cream, a 7 day treatment regimen.

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), days 15-19 (return visit 1 - RV1) and days 35-43 (return visit 2 - RV2).

In both studies the primary parameter used to determine overall efficacy was therapeutic cure. Clinical cure and microbiologic cure were independently evaluated in these studies. As previously noted therapeutic cure was the composite of both the clinical and microbiologic effects (See table 4).

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 Monistat 1 (1200 mg ) and external cream  
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Table 4

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 bismuth, glucose, glycine, yeast extract agar (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 were not noted. Specimens for fungal culture were inoculated onto BiGGY agar plates and incubated at 30°C for 5 days. On this medium growth of brown to black colonies was 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 and species identification was not performed in these studies.

**The Sponsor's results from clinical trial 96-002-P:**

Table 5 shows the sponsor's analysis of the clinical, microbiologic and therapeutic cure rates for patients enrolled in trial 96-002-P. At the end of therapy (return visit 2) 71.7% versus 70.1% of the patients receiving the 1200 mg  and the 2% miconazole cream, respectively, were classified as a

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Advanced Care Products

therapeutic cure. The overall microbiologic cure rates were 75.8% and 73.2% for patients receiving the 1200 mg miconazole ovule and the 2% miconazole nitrate cream for 7 days, respectively.

Table 5

Table V  
Summary of Overall Cure Rates by Treatment Group,  
Patients Valid for Overall Efficacy

Type of Cure	Treatment Group				P-value*
	Miconazole Nitrate (1200 mg) Vaginal [redacted] N=99		MONISTAT® 7 Vaginal Cream N=97		
	n	%	n	%	
Clinical	81	81.8	79	81.4	0.96
Microbiological	75	75.8	71	73.2	
Therapeutic	71	71.7	68	70.1	

Cross Reference: TABLES 11 and 12b, pages 52 and 56

\* The Cochran Mantel Haenszel Test, stratified by investigator, was used to detect any difference between the treatment groups.

**The Sponsor's Results for Clinical Trial 97-006-P:**

Table 6 shows the sponsor's assessment of the overall cure rates for patients evaluated at the end of clinical trial 97-006-P, RV2. At the end of this study (RV2) the therapeutic cure rates were 69.2% and 70.0% for subjects receiving the 1 day 1200 mg [redacted] and the 7 day 2% miconazole cream, respectively. The overall microbiologic cure rates for patients receiving the single 1200 mg miconazole ovule and the 2% miconazole nitrate cream for 7 days were 69.2% and 68.9%, respectively.

Table 6

Summary of Overall Cure Rates by Treatment Group  
Patients Valid for Overall Efficacy

Overall Cure Rate	Miconazole Nitrate (1200 mg) Vaginal [redacted] (N = 104)		MONISTAT® 7 Vaginal Cream (N = 90)	
	n	%	n	%
Clinical	72	69.2	63	70.0
Microbiological	72	69.2	62	68.9
Therapeutic	64	61.5	55	61.1

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Monistat 1 (1200 mg [redacted] and external cream  
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The remaining evaluable subjects in both studies were classified as either a microbiologic failure (KOH and/or culture positive at RV2) or a relapse (negative microbiology at RV2 and positive microbiology at RV3). Table 7 shows the number of subjects that were classified as microbiologic failures or relapses.

Table 7

Microbiologic Results of Evaluable Patients  
in Studies 96-002 and 97-006

Study	96-002		97-006	
	Miconazole Nitrate [redacted] 2% cr		Miconazole Nitrate [redacted] 2% cr	
Treatment Regimen # Patients (%)				
Total # evaluable pts	99	97	104	90
Microbiologic Cures	75 (75.8)	71 (73.2)	72 (69.2)	62 (68.9)
Microbiologic Failures	13 (13.1)	8 (8.1)	22 (15.7)	16 (17.8)
Microbiologic Relapses	11 (11.0)	18 (18.6)	8 (7.7)	10 (11.1)
Microbiologic Non-evaluable pts (no RV2 micro)	0 (0)	0 (0)	2 (1.9)	2 (2.2)

Comments:

Because the fungal strains were not speciated and susceptibility testing was not conducted in either study the exact reason for microbiologic non-response (i.e. failure or relapse) could not be discerned. The assessment of the fungal species and the susceptibility test results would be useful in differentiating relapse of disease, recolonization or the

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occurrence of a new infection. As a result, the cause of the microbiologic failures obtained from subjects enrolled in these clinical trials cannot be determined. It is highly recommended that in all future clinical trials all fungal isolates be speciated and susceptibility testing be conducted on all pre- and post-treatment isolates to evaluate drug resistance development.

References:

1. Cotton, 1994. AIDS in Women. Textbook of AIDS Medicine. Williams and Wilkins. Chapter 11:161-168.D.
2. Sobel. 1994. Controversial aspects in the management of vulvovaginal candidiasis. J. Am. Acad. Dermatol. S10-13.
3. Sobel. 1992. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. Clin. Infect. Dis. 4:S48-52.
4. Carpenter, et. al., 1991. Human Immunodeficiency virus infection in North American women: Experience of 200 cases and a Review of the Literature. Medicine. 70:307-325.
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11. Monif, 1985. Classification and pathogenesis of vulvovaginal candidiasis. Am. J. Obstet. Gynecol. 152:935.

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Monistat 1 (1200 mg [redacted]) and external cream  
Advanced Care Products

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

**Labeling:**

In this NDA the sponsor has proposed to market the one day 1200 mg miconazole nitrate vaginal [redacted] for prescription use only. The microbiology review of the proposed label is located in NDA 20968.BL.

**Conclusions:**

Miconazole nitrate is an antifungal azole that is currently approved and marketed in several formulations for the treatment of occasional and recurrent episodes ( $\leq 4$  infections/year) of vulvovaginal candidiasis. In this NDA the sponsor has proposed to incorporate 1200 mg miconazole nitrate into an [redacted] that will be administered intravaginally as a single dose and available for prescription use only.

Preclinical activity data have demonstrated that miconazole has activity against most *Candida* species. As with other antifungal azoles, miconazole has characteristic activity properties. Published articles have reported that drug resistant strains of *Candida albicans* have emerged when antifungal azole therapy is used chronically over long periods of time. In addition, cross resistance between antifungal azoles has been observed with various *Candida* species and yeast strains such as *C. krusei*, *C. glabrata*, *C. parapsilosis* are inherently resistant to antifungal azoles. Trends in clinical trial data evaluating miconazole nitrate cream formulas suggest that there is an increased incidence, though to date, not statistically significant, of inherently resistant strains of *Candida* in patients who relapse or fail therapy.

An indepth microbiologic evaluation of the 1200 mg miconazole [redacted] based on clinical trials 96-002 and 97-006 was not possible given that the fungal pathogens were not speciated and antifungal susceptibility testing was not conducted. The only microbiologic observation that can be made from the clinical trial is that comparable numbers of patients with VVC responded when treated with the 1200 mg miconazole nitrate [redacted] (single dose) compared to the 7 day treatment regimen with 2% miconazole nitrate cream.

To conclude, with respect to microbiology the "monistat dual-pak" containing a single 1200 mg miconazole nitrate vaginal [redacted] with 2% miconazole nitrate external cream is approved for

NDA 20-968

Monistat 1 (1200 mg [redacted]) and external cream  
Advanced Care Products

the treatment of vulvovaginal candidiasis pending final approval of the label.

**Recommendations:**

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

[redacted] /S/

Linda L. Gosey  
Microbiologist (HFD 590)

**Concurrences:**

HFD-590/Dep Dir [redacted] /S/

HFD-590/Micro TL [redacted] /S/

Signature 6/28/99 Date

Signature 6/4/99 Date

**CC:**

- HFD-590/ Orig.NDA#20-968
- HFD-590/ Division File
- HFD-590/MO
- HFD-590/CSO
- HFD-590/Chem
- HFD-590/Pharm
- HFD-590/Review Micro:Gosey

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ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020968**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW**

<b>NDA:</b>	20-968
<b>Submission Date:</b>	June 30, 1998
<b>Drug Product:</b>	Miconazole Nitrate 1200 mg Soft Gel Vaginal Insert and Miconazole Nitrate 2% External Vulvar Cream
<b>Trade Name:</b>	MONISTAT® DUAL-PAK®
<b>Sponsor:</b>	Advanced Care Products (ACP) New Brunswick, NJ
<b>Submission Type:</b>	Original NDA
<b>Category:</b>	S
<b>OCPB Reviewer:</b>	Philip M. Colangelo, Pharm.D., Ph.D.
<b>OCPB Log-In:</b>	July 7, 1998

**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 (VVC). 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. A higher strength 4% (200 mg / 5 gm) MONISTAT® vaginal cream was recently approved in 1998 for direct OTC use for 3-day treatment of VVC.

In this submission, the sponsor is seeking market approval for a miconazole nitrate 1200 mg soft gelatin vaginal insert (also referred to as vaginal ovule), which is to be packaged along with the approved MONISTAT® 2% (100 mg / 5 gm) External Vulvar Cream (9 gm tube). This combination product is to be marketed for prescription use only under the proposed tradename MONISTAT® DUAL-PAK®. It is indicated as a 1-day treatment of vaginal yeast infections (candidiasis) and associated external symptoms, as needed.

As with the other miconazole vaginal products, it appears that the foreign marketing experience with the soft gelatin vaginal ovules is extensive. The miconazole nitrate 1200 mg vaginal [redacted] has been approved for marketing (tradename GYNO-DAKTARIN® 1) in 19 countries outside the U.S.; as prescription use in 15 of these countries and as OTC use in the remaining 4 countries. A 400 mg soft gelatin vaginal [redacted] is also marketed in Canada for 3-day treatment of VVC for a total dose of 1200 mg. Most recently, the same 1200 mg [redacted] that is being sought for approval in this current NDA has been approved for OTC use as a 1-day treatment of VVC in Canada.

**II INDICATIONS AND USAGE**

The proposed labeling for this product is provided as Appendix 1 with this review. The indications and doses are summarized as follows:

*Soft Gelatin Vaginal Insert:* One 1200 mg insert inserted intravaginally at bedtime for local treatment of vulvovaginal candidiasis.

*External Vulvar Cream:* For relief of external vulvar itching and irritation associated with a yeast infection. Sufficient amounts of cream should be applied to cover affected areas twice daily (morning and evening).

### III. SUMMARY

**Item 6: Human Pharmacokinetics and Bioavailability** of this submission contained one drug absorption study, **Protocol 97-007-P**. A more detailed review of this study is provided in **Appendix 2** and is available upon request from the OCPB reviewer or the Division of Pharmaceutical Evaluation 3 (OCPB, DPE 3).

The objective of the study was to evaluate the safety and systemic absorption of miconazole following intravaginal administration of the 1200 mg miconazole nitrate vaginal [redacted] in two parallel groups of young (18-45 yr.) healthy female subjects:

**Group 1: Single Dose Miconazole Nitrate 1200 mg Vaginal [redacted] N = 12.**

PK sampling from predose (0 hr) to 96 hrs postdose, N = 10.

**Group 2: Single Dose Miconazole Nitrate 1200 mg Vaginal [redacted] on Day 1, Then a Second Single Dose of the Miconazole Nitrate Vaginal [redacted] on Day 3 (i.e., at 48 hrs after the first dose), N = 12.**

PK sampling after 1<sup>st</sup> [redacted] from predose (0 hrs) to 48 hrs postdose; after 2<sup>nd</sup> [redacted] from predose (48 hrs after 1<sup>st</sup> dose) to 96 hrs postdose (total of 144 hrs after 1<sup>st</sup> dose), N = 10.

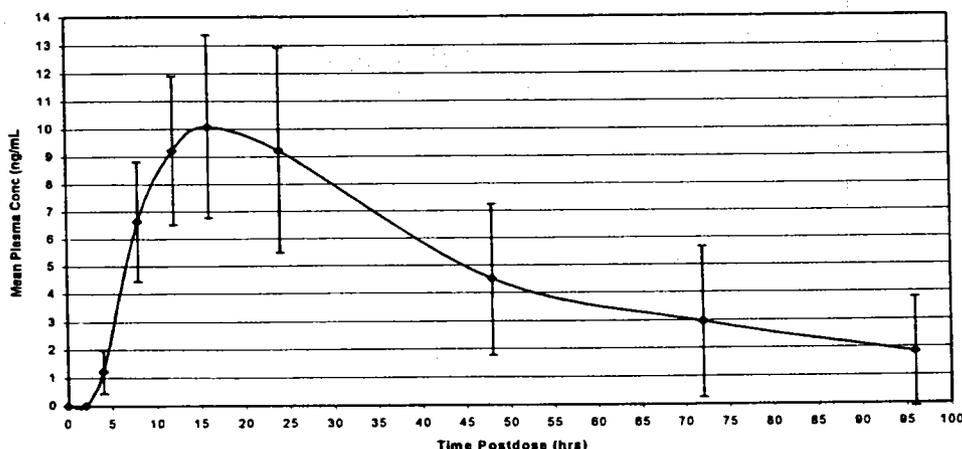
Safety was evaluated in all 12 subjects from each group, while pharmacokinetic (PK) evaluations were performed on 10 of the 12 subjects from each group.

### PHARMACOKINETICS

#### Single [redacted] Administration (Groups 1 and 2)

The mean miconazole plasma concentration-time curve for the 10 **Group 1** subjects is shown in Figure 1 below.

Figure 1: Mean (SD) Miconazole Plasma Concentrations Following Single 1200mg [redacted] Administration - Group 1 (N = 10)



Plasma miconazole concentrations in all **Group 1** subjects were non-quantifiable (<0.250 ng/mL) at predose and 2 hrs postdose, then remained quantifiable out to 96 hrs after single ovule administration. Plasma levels at 24 hrs postdose ranged from 5.0 to 16.8 ng/mL (mean  $\pm$  SD 9.2  $\pm$  3.7 ng/mL, CV 40%). Plasma levels at 96 hrs postdose were highly variable and ranged from 0.3 to 6.3 ng/mL (mean  $\pm$  SD 1.8  $\pm$  1.9 ng/mL, CV 106%).

The PK results in Tables 1 and 2 below showed similar mean and range of parameter values following single ovule administration between **Groups 1** and **2**. This data suggested that drug absorption from the ovule and systemic exposure to miconazole was consistent between the two different groups of female subjects after single intravaginal administration.

**TABLE 1**  
Group 1 Mean Pharmacokinetic Parameters for Miconazole in Plasma Following Single Administration

	AUC(0-24) (ng.hr/mL) n = 10	AUC(0-48) (ng.hr/mL) n = 10	Cmax (ng/mL) n = 10	Tmax (hr) n = 10
Mean	164.5	329.4	10.7	18.4
SD	49.0	101.7	3.14	5.1
Range	84.3-281.5	199.3-544.8	5.8-18.3	12.0-24.0
CV	30%	31%	29%	28%

**TABLE 2**  
Group 2 Mean Pharmacokinetic Parameters for Miconazole in Plasma Following First Administration (Day 1) – All Subjects

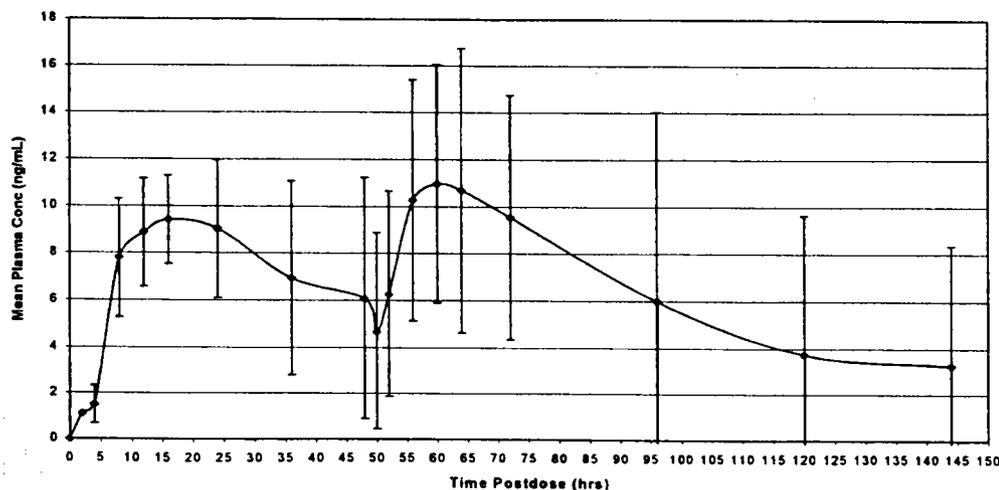
	AUC(0-24) (ng.hr/mL) n = 10	AUC(0-48) (ng.hr/mL) n = 10	Cmax (ng/mL) n = 10	Tmax (hr) n = 10
Mean	164.1	337.9	10.6	17.2
SD	30.5	118.8	2.78	8.7
Range	125.8-231.2	211.2-595.7	7.4-17.1	8.0-36.0
CV	19%	35%	26%	51%

It is also noteworthy to point out the prolonged occurrence of Tmax observed for both groups. The mean Tmax in both groups was 17-18 hrs and ranged from 8-36 hrs. The majority of individual Tmax values occurred at 16-24 hrs, i.e., 8/10 **Group 1** subjects and 6/10 **Group 2** subjects. In one **Group 2** subject (# 02011), maximum miconazole concentrations in plasma were not observed until 36 hrs after the dose. The prolonged Tmax in plasma suggested a slower absorption rate of drug from the ovule into the systemic circulation than what has been observed previously with the miconazole nitrate cream formulations (see formulation comparisons below).

### Repeat Ovule Administration (Group 2)

The mean miconazole plasma concentration-time curve for the 10 **Group 2** subjects is shown in Figure 2 below.

Figure 2: Mean (SD) Miconazole Plasma Concentrations Following Single 1200mg Administration on Day 1 (0 hrs) and on Day 3 (48 hrs) - Group 2 (N = 10)



At the time of the second ovule administration on **Day 3** (i.e., 48 hrs following first ovule administration), plasma concentrations of miconazole showed substantial variability, i.e., mean ( $\pm$  SD) concentration  $6.1 \pm 5.2$  ng/mL (CV 85%); range 1.8 to 18.9 ng/mL. Plasma levels of miconazole remained quantifiable and highly variable through 96 hrs following the second ovule dose (i.e., 144 hrs after first ovule administration), with the mean ( $\pm$  SD) concentration of  $3.2 \pm 5.1$  ng/mL (CV 159%), range 0.71 to 17.4 ng/mL.

The mean PK parameters for **Group 2** after second ovule administration are summarized in Table 3 below.

**TABLE 3**  
Group 2 Mean Pharmacokinetic Parameters for Miconazole in Plasma Following Second Ovule Administration (Day 3) – All Subjects

	AUC(0-24) (ng.hr/mL) n = 10	AUC(0-48) (ng.hr/mL) n = 10	AUC(0-96) (ng.hr/mL) n = 10	Cmax (ng/mL) n = 10	Tmax (hr) n = 10
Mean	221.7	408.3	608.9	12.0	16.0
SD	120.2	277.6	573.9	5.93	11.8
Range	138.5-550.7	208.1-1171	265.6-2206	8.1-28.4	8.0-48.0
CV	54%	68%	94%	49%	74%

Comparison of the **Day 3** to **Day 1** mean AUC(0-24) and AUC(0-48) estimates for **Group 2** suggested modest accumulation (or increase) of miconazole in plasma after second ovule administration of 35% and 21%, respectively. Comparison of the mean AUC(0-96) values for **Group 2, Day 3** and **Group 1** suggested a similar degree of accumulation of 27%. The mean Cmax was increased slightly by 13% after second ovule administration on **Day 3** compared to first ovule administration on **Day 1**, while the mean Tmax values were similar (16 hrs **Day 3** vs. 17 hrs **Day 1**).

The overall variability in the mean PK estimates (as %CV) was greater for the **Group 2** subjects as compared to the **Group 1** subjects, and was particularly pronounced following second ovule administration. This appeared to be mainly due to the PK results obtained for one subject, **02011**. The plasma miconazole concentrations and the resulting PK parameters for **subject 02011** were substantially higher than those for the remaining 9 subjects in **Group 2**. Following first and second ovule administration, this subject's PK values (i.e., AUC, Cmax, and Tmax) were ~2-3 times higher than the parameter values obtained for the other 9 subjects. At 48 hrs after first ovule administration, the plasma miconazole concentration for **subject 02011** was 18.9 ng/mL, while the mean concentration for the remaining 9 subjects was 4.6 ng/mL (~4 times higher). At the last sampling time following second ovule administration (i.e., 96 hrs) the plasma miconazole concentration for **subject 02011** remained elevated at 17.4 ng/mL, while the mean plasma level for the remaining 9 subjects was 1.7 ng/mL (~10 times higher). The accumulation of miconazole in plasma after second administration in **subject 02011** was estimated to be approximately 2 to 3 times of that after single administration (i.e., increase of ~200-300%), as determined by either the AUC(0-24) or AUC(0-48) estimates for this subject.

If the PK data from **subject 02011** are excluded, there was a substantial reduction in the overall variability in the mean PK parameters for **Group 2** (i.e., CV's from ~50-130% decreased to ~20-40%). There was also a reduction in the extent of accumulation of miconazole in plasma after second ovule administration (i.e., accumulation of ~25-35% decreased to <15%).

*Overall, it appeared that the PK data from **subject 02011** had a substantial influence on the between subject variability observed in the PK parameters determined for **Group 2** (i.e., %CV) and on the assessment of the extent of plasma accumulation of miconazole after second administration.*

*The reasons for the higher and prolonged systemic exposure to miconazole in **subject 02011** were not apparent from the study report. There were no apparent physiological*

*abnormalities and no concomitant drug administration was reported. In addition, subject 02011 completed the study and no adverse events were reported following either first or second [redacted] administration.*

**SAFETY**

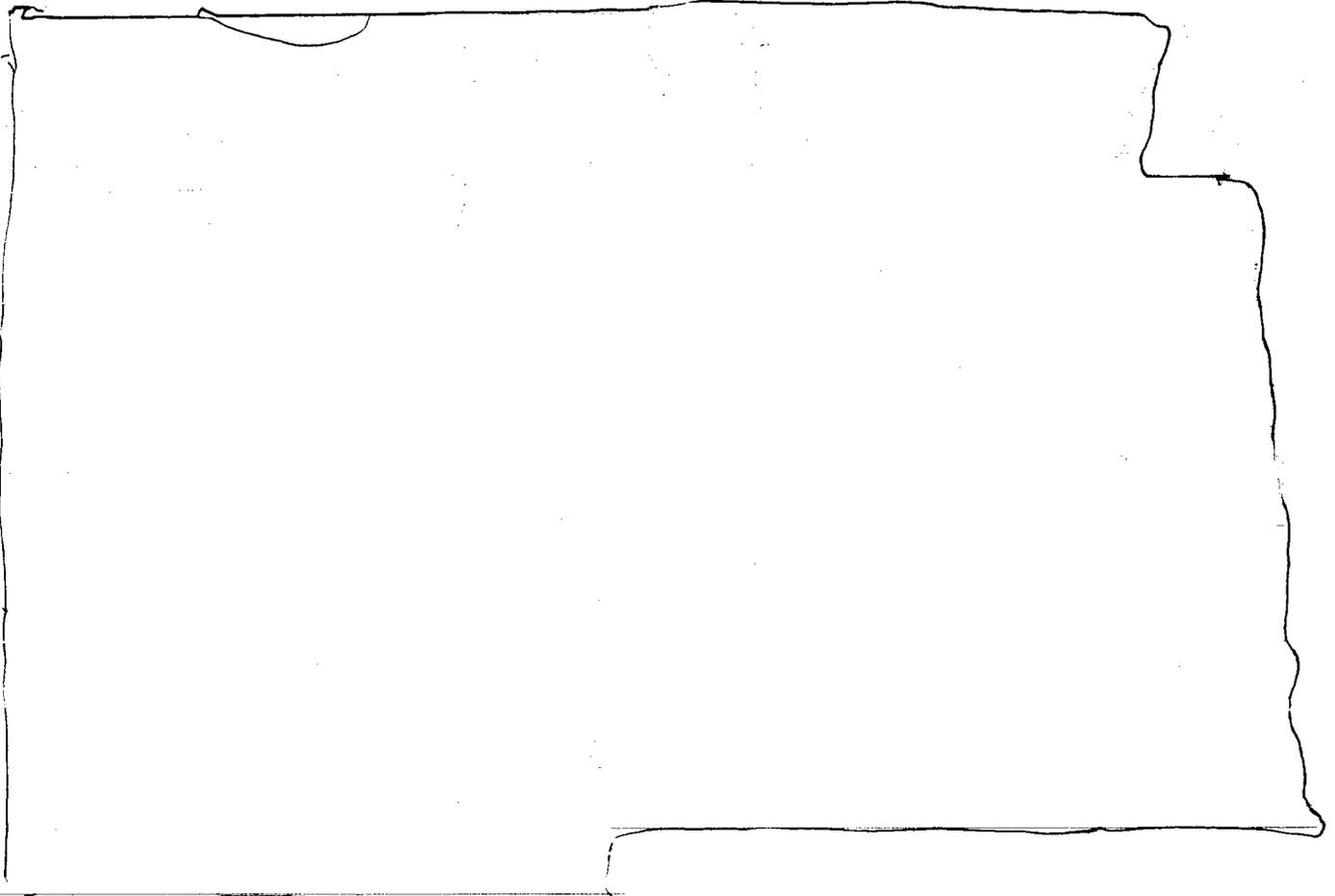
Adverse events (all causalities) were reported for 16/24 subjects; 8/12 from **Group 1** and 8/12 from **Group 2**. The majority of adverse events were of mild to moderate severity and no serious adverse events were reported during the study. One subject from **Group 2 (02008)** withdrew from the study due to an acute anxiety episode, which was judged to be not related to drug.

Three adverse event types were reported by the sponsor with an incidence of >5%:

- (1) mild vaginal burning in 2/10 **Group 1** subjects (highly probable relationship to study drug);
- (2) mild, moderate, or severe headache in 4/10 **Group 1** and 4/10 **Group 2** subjects (possible to unlikely relationship to study drug);
- (3) mild dizziness in 2/10 **Group 1** subjects (possible to unlikely relationship to study drug).

Another group of adverse events observed by the OCPB reviewer may be associated with the gastrointestinal system and included the following single subject complaints, all reported from **Group 2**: mild constipation (possibly related), mild loose stool (probably related), mild indigestion (possibly related), and mild lower abdominal cramping (possibly related).

*Overall, it appeared that single or repeated [redacted] administration was well tolerated in the two groups of female subjects.*





**IV. RECOMMENDATION**

Item 6 (Human Pharmacokinetics and Bioavailability) of NDA 20-968 for MONISTAT® DUAL-PAK has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been deemed to be acceptable. The comments provided below need to be conveyed to and adequately addressed by the sponsor.

**V. COMMENTS FOR THE SPONSOR**

1. There are concerns over the use of the PK modeling and simulation results in the **Human Pharmacology** portion of the proposed labeling. The statement that systemic exposure to miconazole after single [redacted] administration was only marginally increased (i.e., by 13%) as compared to after 7 days of therapy with the MONISTAT® 7 original base vaginal cream was based on *predicted* estimates of AUC derived from the PK modeling and simulation of plasma miconazole concentration-time profiles. However, the results from the current and previous NDA absorption studies showed that the mean AUC (and Cmax) estimates for the ovule were substantially greater than those obtained after 7 doses of the MONISTAT® 7 (M-7) original base vaginal cream, i.e., ~4-5 times higher.

There is concern over the similarity of the model parameter estimates of  $\lambda_1$  (0.077254 hr<sup>-1</sup>) and  $\lambda_2$  (0.076996 hr<sup>-1</sup>) reported for the fit of the data for the M-7 cream. Based on inspection of the predicted concentration-time profile in Figure VI of the PK study report for study 97-007-P, it would appear that the estimate of  $\lambda_2$  would need to be smaller than that of  $\lambda_1$  in order for the reported estimates of A1 (12.52) and A2 (3.346) to be correct. If the reported estimates for  $\lambda_1$  (0.077254 hr<sup>-1</sup>) and  $\lambda_2$  (0.076996 hr<sup>-1</sup>) are indeed correct, then one would expect the model to predict similar values for A1 and A2, and consequently, a one-compartment model would be the best fit model to describe the data for the cream. **The Agency would like clarification from the sponsor regarding this concern. Comparisons of systemic drug exposure between the [redacted] and the cream formulations should be based on actual, observed AUC values, rather than on the predicted estimates of systemic exposure. Thus, it is recommended that the proposed label be edited to delete the statements concerning the modeling results.**

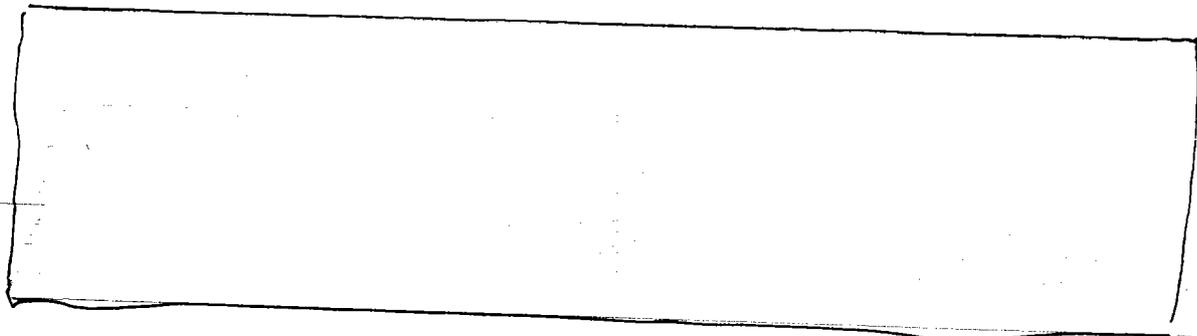
2. The methods to evaluate disintegration of the [redacted] during stability testing and as part of the specifications for release of commercial batches of the bulk [redacted]

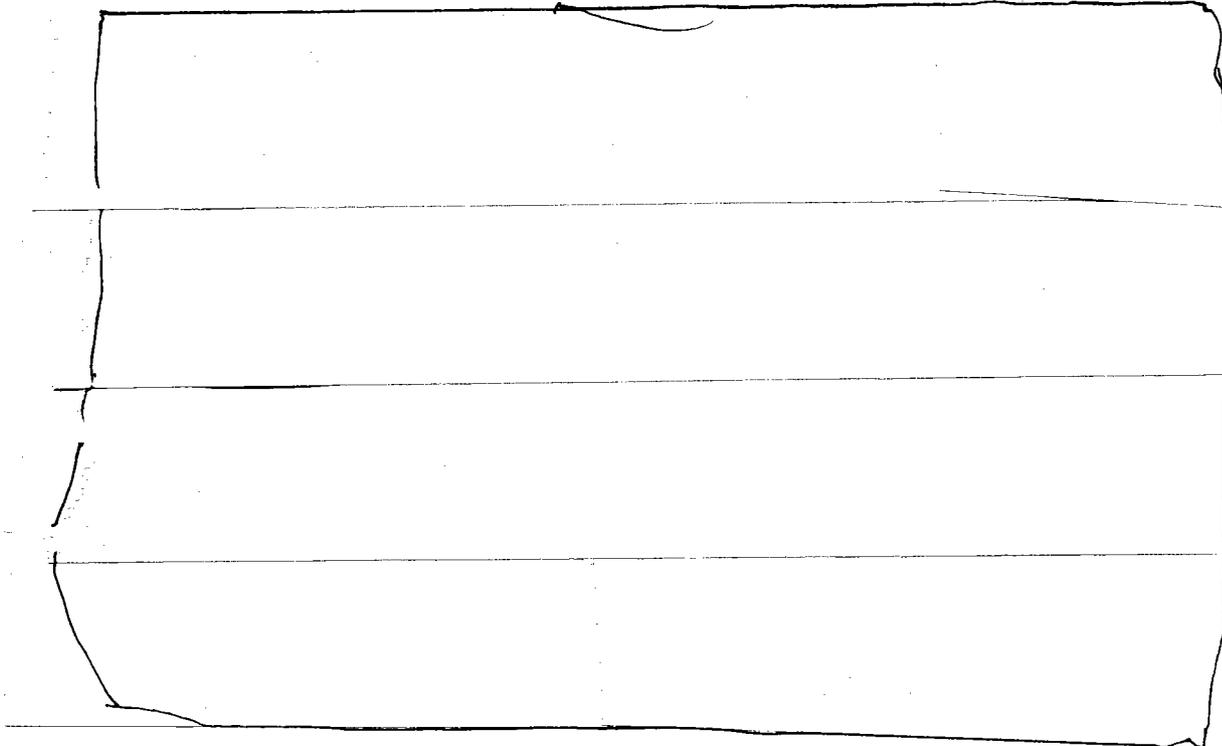
**The Agency finds this method acceptable.**

**The proposed specification is disintegration in [redacted] Based on the disintegration results with the [redacted] batches in the stability study [redacted] it is recommended that the proposed specification of [redacted] be [redacted]**

**VI. LABELING COMMENTS**

See Appendix 1 attached with this review.





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ON ORIGINAL

[Redacted] /S/ 6/1/99

Philip M. Colangelo, Pharm.D., Ph.D.  
Office Clinical Pharmacology/Biopharmaceutics,  
Division of Pharmaceutical Evaluation 3

RD/FT signed by Funmi Ajayi, Ph.D (TL)

[Redacted] /S/ 6/1/99

CP/B Briefing Attendees (5/19/99): J. Lazor, A. Selen, F. Ajayi, F. Pelsor, K. Reynolds, E.D. Bashaw, H. Sun, K. Uhl, E. Cox

cc:  
HFD-590 (Div. File): NDA 20-968  
HFD-590 (E. Cox, MO)  
HFD-590 (C. Chi, PM/CSO)

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HFD-205 (FOI)  
HFD-880 (F. Ajayi)  
HFD-880 (P. Colangelo – NO COPY NEEDED)  
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CDR (Barbara Murphy – NO COPY NEEDED)

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**APPENDIX 1**

**PROPOSED LABELING (v: 5/7/99)  
WITH  
CLINICAL PHARMACOLOGY / BIOPHARMACUETICS COMMENTS**

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DRAFT LABELING