CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020968

MEDICAL REVIEW(S)

JUN 30 1999

Addendum to the Medical Officer's Review of NDA 20-968

1. General Information

1.1. NDA 20-968

1.2. Applicant identification

Advanced Care Products, Personal Products Company
199 Grandview Road
Skillman, New Jersey 08558-9418
Tel. (732) 524-1675
Fax. (732) 732-1344

Name of contact person or company official — Diane Herron, Director, Regulatory Affairs

1.3. Submission/review dates

Date of submission of NDA: June 30, 1998
CDER stamp date of NDA: June 30, 1998
Date of submission amendment: June 24,1999
Date of MOR Addendum: June 29, 1999

1.4. Drug identification

Generic name: miconazole nitrate
Proposed trade name: MONISTAT® DUAL-PAK®
Chemical name: 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy] phenethyl] imidazole mononitrate
Molecular formula: $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$
Molecular weight: 479.15

1.5. Pharmacologic category: synthetic imidazole antifungal agent

1.6. Dosage form: 1200 mg soft gel vaginal insert and 2% external vulvar cream

1.7. Route of administration: intravaginal (gel insert) and topically (external vulvar cream)

Subject: Review of Advanced Care Products correspondence dated 6/24/99, in which the Applicant proposes the following changes to the "When can I expect symptom relief?" section of the PATIENT PACKAGE INSERT:

When can I expect symptom relief? (Applicant's proposed revisions)

While the MONISTAT® DUAL-PAK™ includes a single-dose vaginal insert, most women do not get complete relief of their symptoms in just 1 day. Most women experience some improvement within 1 day and complete relief of symptoms within 7 days. If your symptoms do not improve in 3 days, or if you still have symptoms after 7 days, call your health professional.

MO Comment/Recommendation: There is no analysis in the NDA to support the claim that "most women experience some improvement within 1 day." Therefore, the MO recommends removal of this statement. The MO recommends that the word "most" should be changed to the word "majority" in the statement that "most women experience complete relief of symptoms within 7 days." The statement "the majority of women experience complete relief of symptoms within 7 days" is supported by a validated version of the Applicant's analysis of "days to relief of itching and burning" performed by the Biostatistical Reviewer, Dr. Cheryl Dixon. Furthermore, this statement is consistent with the standard statement in the label that patients not experiencing relief after 7days should contact their health professional.

During a teleconference of June 25, 1999, the Applicant and the Agency proposed the following revisions to the "When can I expect symptom relief?" section of the PATIENT PACKAGE INSERT:

When can I expect symptom relief?

While the MONISTAT® DUAL-PAK™ includes a single-dose vaginal insert, most women do not get complete relief of their symptoms in just 1 day. The majority of women experience complete relief of symptoms within 7 days. While you are waiting for the infection to clear, the external vulvar cream can be used to soothe and relieve the itching and irritation outside the vagina. If your symptoms do not improve in 3 days, or if you still have symptoms after 7 days, call your health professional.

MO Comment: The statement "While you are waiting for the infection to clear, the external vulvar cream can be used to soothe and relieve the itching and irritation outside the vagina" is consistent with the indication for the MONISTAT® External Vulvar Cream. The version of "When can I expect symptom relief?" that immediately precedes this MO Comment is in the final version of the PATIENT PACKAGE INSERT.

APPEARS THIS WAY ON ORIGINAL

/S/ [redacted] 6/29/99

Edward M. Cox, Jr., M.D.
Reviewing Medical Officer/HFD-590

cc: Division File
NDA 20-968

HFD-590/DepDir/RAlbrecht
HFD-590/MTL/BLeissa/S/ [redacted] 6/29/99
HFD-590/MO/ECox
HFD-590/PharmTox/OMcMaster
HFD-590/Micro/LGosey
HFD-590/Chem/DMatecka
HFD-590/CSO/CChi
HFD-880/BioPharm/PColangelo
HFD-725/Stat/CDixon
HFD-40/SpearmonJ

Concurrence Only:
HFD-590/DivDir/MGoldberger /S/ [redacted] 6/30/1999

APPEARS THIS WAY ON ORIGINAL

DFS Keywords
Admin: review
Drug class: class antifungal, class topical anti-infectives
Indication: indic candidiasis vulvovaginal
Special populations: pop adult

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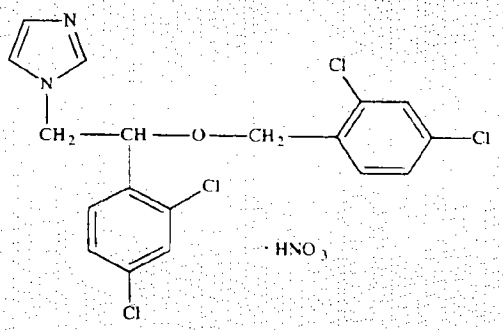
Name of contact person or company official — Diane Herron, Director, Regulatory Affairs

1.3. Submission/review dates

Date of Submission: June 30, 1998
CDER stamp date: June 30, 1998
Date submission received by reviewer: August 31, 1998
Date review begun: September 1, 1998
Date review completed: June 17, 1999

1.4. Drug identification

Generic name: miconazole nitrate
Proposed trade name: MONISTAT® DUAL-PAK®
Chemical name: 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy] phenethyl] imidazole mononitrate
Chemical structure:



Molecular formula: $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$
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Note: The Times New Roman font is used in this document to represent text copied verbatim from the Applicant's NDA

1.8. Proposed INDICATIONS AND USAGE section

DRAFT LABELING

1.9. Proposed DOSAGE AND ADMINISTRATION section:

DRAFT LABELING

1.10. Proposed CLINICAL STUDIES section:

DRAFT LABELING

1.11.Related NDAs of miconazole nitrate products for the treatment of vulvovaginal candidiasis

Table 1. Related NDAs of Miconazole Nitrate Products for VVC

NDA	Year of Approval	Year of Approval for OTC use	Name	Dosage Form	Dose	Duration of Therapy
17-450	1974	1991	MONISTAT-7 Vaginal Cream	2% vaginal cream	100 mg qd	14 days
	1977		MONISTAT-7 Vaginal Cream	2% vaginal cream	100 mg qd	7 days
18-520	1982	1991	MONISTAT-7 Vaginal Suppositories	100 mg vaginal suppository	100 mg qd	7 days
18-592	1989	—	MONISTAT-5 Tampons	100 mg tampon	100 mg qd	5 days
18-888	1984	—	MONISTAT-3 Vaginal Suppositories	200 mg vaginal suppository	200 mg qd	3 days
20-288	1993	1993	MONISTAT-7 Combination Pack	100 mg vaginal suppository and external vulvar cream	100 mg qd (suppository)	7 days
20-670	1996	1996	MONISTAT-3 Combination Pack	200 mg vaginal suppository and external vulvar cream	200 mg qd (suppository)	3 days
20-827	1998	1998	MONISTAT-3	4% vaginal cream	200 mg qd	3 days

MO Comment: The currently marketed over-the-counter (OTC) product, MONISTAT-1®, uses tioconazole as its active ingredient.

1.12.Material reviewed

NDA volumes reviewed 1.1, 1.9-1.11, 1.15-1.29
Amendment 4.1
Revised draft labeling submitted April 19, 1999 and May 7, 1999
Other documents reviewed applicable to this review
Medical Officer's Review of NDA 20-827 (MONISTAT®3 Vaginal Cream (4%))
Medical Officer's Review of NDA 20-574 (Gyne-Lotrimin-3™ Vaginal Cream (2%))
IND [redacted]

1.13. Regulatory background

Vulvovaginal candidiasis (VVC) is estimated to be the second most common vaginal infection in North America.[1] It is estimated that up to 75% of all pre-menopausal women will experience at least one episode of VVC.[2] *Candida albicans* causes most of these cases of VVC. A number of therapies are available for the treatment of VVC including both topically and orally administered therapies.

The IDSA/FDA Guidelines for the Clinical Evaluation of Anti-Infective Drug Products 1992, provides guidance on the evaluation of anti-infective drug products for the treatment of yeast vulvovaginitis. The recommendations include the establishment of the diagnosis by both clinical and laboratory techniques. The authors caution that vulvovaginal infections can present with similar symptoms, therefore definitive establishment of the diagnosis is essential in clinical trials. The diagnostic criteria for yeast vulvovaginitis should include *(a) signs or symptoms of a vulvar or vaginal disorder; (b) demonstration of yeasts or pseudomycelia in a suspension in saline or 10% KOH by gram staining or by culture of Candida or other yeasts from vaginal secretions; and (c) exclusion of other causes of vulvovaginal symptoms.*[3] The IDSA/FDA guidelines recommend the following for patients with yeast vulvovaginitis participating in clinical trials: *(1) physical examination of the vulva, vagina, cervix, and internal reproductive organs, by inspection and palpation, with description of secretions: (2) cervical and rectal cultures for N.gonorrhoeae and cervical culture or nonculture test for C. trachomatis (these may be omitted for patients with yeast vulvovaginitis who are at low risk for STDs); (3) microscopic examination of vaginal secretions (gram staining and suspension in saline and 10% KOH) for clue cells, yeasts, trichomonads, leukocytes, and (in studies of bacterial vaginosis) bacterial morphotypes; (4) culture and identification of yeasts on either selective or nonselective media (e.g. blood agar); (5) culture for T.vaginalis; (6) determination of vaginal pH by direct application of secretions onto a colorimetric pH indicator; (7) an amine odor ("whiff") test; and (8) quantitative urine culture (when patients have dysuria or other symptoms suggestive of bacterial urinary tract infection).*[3]

In order to meet the inclusion criteria for a clinical trial studying yeast vulvovaginitis, the IDSA/FDA guidelines require that both clinical and microbiological criteria be met. The clinical criteria require that the patient have signs or symptoms of vulvovaginitis. The microbiological criteria require that *a yeast (usually Candida species) must be grown from vulvovaginal secretions; microscopic*

identification of yeasts or pseudomycelia is adequate for enrollment.[3] The guidelines recommend that the subjects studied generally should be otherwise-healthy women of at least 18 years of age. The Guidelines recommend that the following patients should be excluded (unless they are specifically targeted by the study): women with coexisting conditions that require antimicrobial therapy, women using medications that will alter the pharmacokinetics or response to the test agent, women with coexisting immunodeficiency, women who are pregnant or nursing.

The guidelines recommend that the comparator agent chosen should be selected from among the most effective FDA-approved and CDC recommended drugs for the indication under study. The clinical trial should be randomized and controlled because of the often imprecise nature of the clinical endpoints. In addition, a double-blind study design should be used to reduce both patient and investigator bias.

> **MO Comment:** More recent draft guidance from the FDA recommends that placebo not be employed because of the potential interference from co-administration of a second topical agent.[4]

The IDSA/FDA guidelines recommend that outcomes be measured in an intent-to-treat analysis, and analyses of clinical and microbiological response.[5]

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[1]Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol 1998; 178(2):203-211.

[2]Sobel JD. Vaginitis. NEJM 1997;337(26) 1896-1903.

[3]McCutchan JA, Ronald AR, Corey L, Handsfield HH. Evaluation of new anti-infective drugs for the treatment of vaginal infections. Clin Infect Dis 1992;15(suppl 1):S115-S122.

[4]Guidance for Industry (Draft Guidance): Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment. US DHHS, FDA, CDER, July 1998.

[5]Beam, Jr. TR, Gilbert DN, Kunin, CM . General guidelines for the clinical evaluation of anti-infective drug products. Clin Infect Dis 1992;15(suppl 1):S5-S32.

2. Table of Contents

3. Chemistry/Manufacturing Controls

Miconazole nitrate drug substance is manufactured by [redacted] Manufactured drug product is tested for purity, quality, and identity to verify conformance with USP requirements. The MONISTAT® Soft Gel Vaginal Insert will be manufactured by [redacted] The process is the same as the manufacturing process for the currently marketed [redacted] The Applicant notes one difference in the drug manufacturing process in the US will be the absence of preservatives in the vaginal ovule gelatin shell. Because of "state-of-the-art technology" available in the US production facility, preservatives are not necessary. The US drug product will be composed of raw materials sourced entirely from the US. [redacted] will manufacture the MONISTAT External Vulvar Cream. The Applicant notes that the product was approved under NDA 17-450 (SCF-043) (MONISTAT® 7 Vaginal Cream supplement).

The source of the drug product used in the major clinical trials in support of this NDA is as follows. For study 96-002 a commercial batch of [redacted] was used. In studies 97-006 and 97-007 the study drug was produced using a scale-up batch prepared by [redacted]

MO Comment: The Chemistry Reviewer, Dr. Matecka has reviewed the composition of the 1200 mg [redacted] used in the pivotal clinical trials. The slight differences in the manufacturing process and the composition of the [redacted] would not be expected to influence the activity of the 1200 mg [redacted]. Please see her review for a full discussion of this issue.

4. Animal Pharmacology/Toxicology

Preclinical animal studies in a variety of animal species have been performed by the Applicant in support of the current and prior NDAs for miconazole products. Studies of acute toxicity following intravenous administration have determined the LD_{50} of miconazole to be in the range of 60-100 mg/kg for mice, rats, guinea pigs, and dogs. Acute toxicity in mice, rats, guinea pigs, and dogs was demonstrated following single oral doses of miconazole ≥ 160 mg/kg. A study of acute toxicity of a 46% miconazole nitrate (MCN) ointment administered orally to rats at a dose of 5 g/kg found an LD_{50} > 2300mg/kg. Single dose studies of topical administration of a 46% MCN ointment to rabbits demonstrated an LD_{50} > 920mg/kg.

Chronic toxicity studies in rabbits ranging over a 6 week to 6 month time period did not show toxicity at doses of miconazole base administered intravenously in doses up to 20 mg/kg/day. Similar studies in dogs for 4 weeks did not demonstrate toxicity at doses up to 40 mg/kg/day administered intravenously. Multidose studies of oral administration of miconazole to dogs performed over 13 weeks and 12 months demonstrated histopathologic changes in the liver at the higher doses studied. In the 13-week study dogs receiving 40 mg/kg developed histopathologic evidence of cloudy swelling with hyaline degeneration of the hepatocytes. In the 12-month study of oral administration, increased liver weight with normal histology was observed in the group of dogs receiving 20 mg/kg/day. Studies of multidose intravaginal administration for 10, 28, and 90 days in rabbits showed minimal to moderate vaginal mucosal or epithelial irritation. Miconazole nitrate (MCN) doses examined in the intravaginal administration studies were 1 g of a 2% suppository, 1 g or 1 mL of 4% cream, or 1 mL of 46% ointment.

Studies of the 46% ointment in the rabbit eye irritation and dermal irritation models found the preparation to be non-irritating. Studies of other MCN preparations have found the preparations to be non-irritating to mildly irritating. Sensitization studies in the guinea pig model found no potential to produce delayed contact sensitization.

Animal reproductive studies of MCN preparations in rabbits and rats did not demonstrate effects on pregnancy rate, spermatotoxicity, or teratogenicity. At doses of 80 mg/kg/day in rabbits the number of resorbed fetuses was increased and maternal and fetal toxicity was observed. In rats at the 80 mg/kg/dose, prolonged gestation and an increased number of stillborn pups was noted. Studies have not demonstrated evidence of mutagenic potential for miconazole.

5. Microbiology

Miconazole is a synthetic imidazole-derivative antifungal agent. It has activity against many pathogenic fungi and yeasts including *Candida* spp. It also has activity against some gram-positive bacteria. The mechanism of action involves the inhibition of ergosterol synthesis with resulting increased cell membrane permeability and loss of intracellular material. Miconazole can inhibit fungal growth and can also achieve fungicidal activity at higher concentrations.

In the current submission, the Applicant presents data on the minimum inhibitory concentration (MIC) determinations for a number of *Candida* isolates (Table 2.) Three of the isolates tested demonstrated MICs in excess of 10 mcg/mL. The Applicant also describes data from a clinical study of women with recurrent VVC searching for evidence of fungal resistance as a possible contributing factor. In this study by Lynch and colleagues analysis of the MICs for fungal isolates of women with

recurrent VVC did not demonstrate *in vitro* resistance. In addition, successive isolates over time from patients on long-term therapy did not demonstrate the development of *in vitro* resistance.[1]

[1]Lynch ME, Sobel JD, Fidel Jr. PL. Role of antifungal drug resistance in the pathogenesis of recurrent vulvovaginal candidiasis. J of Med and Vet Mycology;34:337-339

Table 2. Minimum Inhibitory Concentration for *Candida* Isolates from Janssen Pharmaceutica (Report R 14889/12)

Species	Number of strains tested	Cumulative Proportion of Strains Inhibited by Selected Miconazole Nitrate Concentrations (mcg/mL)				
		0.01 mcg/mL	0.1 mcg/mL	1.0 mcg/mL	10 mcg/mL	100 mcg/mL
C. albicans	1328	52/1328 3.9%	207/1328 15.6%	885/1328 66.6%	1326/1328 99.8%	1327/1328 99.9%
C. tropicalis	76	0/76 0.0%	12/76 15.8%	49/76 64.5%	76/76 100.0%	76/76 100.0%
C. parapsilosis	74	0/74 0.0%	21/74 28.4%	60/74 81.1%	74/74 100.0%	74/74 100.0%
C. krusei	45	1/45 2.2%	6/45 13.3%	25/45 55.5%	45/45 100.0%	45/45 100.0%
T. glabrata	217	2/217 0.9%	10/217 4.6%	173/217 79.7%	216/217 99.5%	217/217 100.0%

(modified from the Applicant's table Vol. 1.1, p. 02-000058)

6. Human Pharmacokinetics/Pharmacodynamics

The Applicant conducted a pharmacokinetic study (study 97-007) to determine the extent of systemic absorption of miconazole following the administration of the 1200 mg soft gel vaginal insert. Systemic absorption following the administration of a second 1200 mg vaginal insert administered 48 hours after the first was also studied to gather pharmacokinetic data if improper use of the product were to occur. This study is reviewed in the section on individual clinical trials. Please also see Dr. Philip Colangelo's Biopharmaceutics review of this study.

7. Human Clinical Experience

7.1. US Post-Marketing Experience

MONISTAT® Vaginal Cream (100mg) was initially approved in the US for prescription use in 1974 as a 14-day course of therapy for VVC. In 1977 the same 100 mg cream formulation was approved for 7-day therapy for treatment of VVC. Subsequently other MONISTAT® formulations have been approved for the treatment of VVC. The year of approval of these other formulations and their subsequent approval for OTC use is presented in Table 1.

When MONISTAT® products began being marketed OTC, a toll-free 800 number was included in the educational brochure. Advanced Care Products has collected the reports of patient adverse experiences from the toll-free number. The Applicant notes that most of the reports are vulvovaginal in nature and approximately 70% occur within the first 3 days of therapy. The number of reports of adverse experiences (AEs) for the AEs contained in the product label are presented in Table 3. Approximately 10 million units of MONISTAT® products have been sold annually since 1991 (which provides an estimate of the denominator for the AEs reported to the toll-free number). The applicant also notes that the number of AEs reported annually has declined over time despite relatively constant sales of MONISTAT® products in the US.

TABLE 3
CONSUMER ADVERSE EXPERIENCE REPORTS (U.S.)
REACTIONS CONTAINED IN LABELING
MONISTAT® 7 VAGINAL PRODUCTS

ADVERSE EXPERIENCE	1991 (N=1869) (%)	1992 (N=1744) (%)	1993 (N=1098) (%)	1994 (N=834) (%)	1995 (N=781) (%)	1996 (N=882) (%)	1997* (N=485) (%)
Burning	587 (31.4)	606 (34.7)	466 (42.4)	289 (34.7)	294 (37.6)	261 (29.6)	170 (35.1)
Itching	236 (12.6)	188 (10.8)	115 (10.5)	77 (9.2)	105 (13.4)	76 (8.6)	45 (9.3)
Fever	35 (1.9)	8 (0.5)	6 (0.5)	4 (0.5)	2 (0.3)	8 (0.9)	2 (0.4)
Back/Shoulder Pain	62 (3.3)	23 (1.3)	10 (0.9)	13 (1.6)	4 (0.5)	20 (2.3)	5 (1.0)
Lower Abdominal Pain (Abdominal/Pelvic/Pain/ Cramping)	161 (8.6)	104 (6.0)	45 (4.1)	38 (4.6)	50 (6.4)	58 (6.6)	21 (4.3)
Headaches	84 (4.5)	44 (2.5)	21 (1.9)	18 (2.2)	16 (2.0)	27 (3.1)	9 (1.9)
Hives/Skin Rash	132 (7.1)	137 (7.9)	87 (7.9)	77 (9.2)	62 (7.9)	61 (6.9)	30 (6.2)

* 1997 Data only represents MONISTAT® 7 VAGINAL CREAM and not MONISTAT® 7 COMBO PACK or MONISTAT® 7 VAGINAL SUPPOSITORIES
(Applicant's Table 1 from p. 08-000599)

In 1996 the MONISTAT®3 Combination Pack was approved as an OTC product and was launched in May of 1996. Adverse experiences reported to the toll-free number were collected and events reflecting AEs in the label are presented in Table 4. In 1997 4.5 million units of the MONISTAT®3 Combination Pack were sold (which allows one to estimate the denominator for the AEs reported to the toll-free number in 1997).

TABLE 4
CONSUMER ADVERSE EXPERIENCE REPORTS (U.S.)
MONISTAT®3 COMBINATION PACK
MAY, 1996-DECEMBER 1997

	May-Dec 1996 N=409		Jan-Dec 1997 N=456	
Adverse Experience	**# of complaints**	**% of total complaints**	**# of complaints**	**% of total complaints**
Burning	109	19.0	114	18.4
Itching	39	6.8	45	7.3
Fever	3	0.5	1	0.2
Back/Shoulder pain	5	0.9	6	0.96
Abdominal/Pelvic Pain/Cramping	33	5.7	31	5
Headaches	7	1.2	6	0.96
Hives/Skin Rash	16	2.8	26	4.2
Lack of Efficacy	197	34.3	227	36.6

(Applicant's Table 2. from p. 08-000600)

Comparing the rates of reporting of the AEs per units sold finds roughly comparable rates for the AEs tabulated for the MONISTAT®3 and MONISTAT®7 products. The Applicant notes that the reports of "lack of efficacy" reported for the 3-day product is higher than that observed for the 7-day products. The Applicant postulates that the greater number of reports of lack of efficacy may be secondary to higher patient expectations or lack of experience with shorter course therapy. The applicant notes that shorter course therapy does not result in a shorter time to the resolution of symptoms.

7.2. Foreign Post-Marketing Experience

Products for the treatment of vulvovaginal candidiasis using miconazole nitrate as their active ingredient are available in 94 countries and are available without a prescription in 34 of these countries. The Applicant estimates that from 1981 until August of 1996 over 41 million patients (excluding the US) have been treated for vulvovaginal candidiasis with miconazole containing products. Based on reports of suspected adverse events, the Applicant estimates a frequency of reported adverse events for miconazole containing preparations of 1 in 160,000 and 1 in 1.5 million for serious adverse events. The Applicant notes that the majority of adverse experiences are local irritation/pain/burning at the site of application. New adverse experiences reported include the interaction of marketed formulations with latex condoms and abdominal/pelvic cramping associated with drug administration.

Table 5. Number of adverse experiences reported* for MONISTAT® products per number of units sold in Canada 1995-1997.

Formulation	Adverse Experiences(AE)/Units Sold (rate per 100,000 units sold)		Total AEs/Units Sold (rate per 100,000)
	Irritation	Other	
MONISTAT® 3 [redacted]	141/619,580 (22.75)	8/619,580 (1.29)	
MONISTAT® 3 COMBINATION PACK¥	269/1,241,284 (21.67)	9/1,241,284 (0.72)	
MONISTAT® 7 SUPPOSITORIES	4/177,822 (2.24)	3/177,822 (1.68)	
MONISTAT® 7 COMBINATION PACK◊	6/208,539 (2.87)	2/208,539 (0.95)	
MONISTAT® 7 CREAM	32/703,039 (4.55)	6/703,039 (0.85)	
TOTAL	452/2,923,624 (15.46)	28/2,923,624 (0.95)	

*Adverse experiences were collected by providing an 800-telephone number on the packaging for consumer reporting

¥ The MONISTAT® 3 preparation in Canada is a 400 mg ovule

◊ Data are limited to 1995 and 1996 for the MONISTAT® 7 Combination Pack

(Adapted from the Applicant's Table 5., Vol. 1.1, p. 02-000019)

The single dose 1200 mg soft gel vaginal insert described in this NDA has been approved for marketing in 19 countries. It was first approved in Denmark in 1982. In four of these countries the product is available without a prescription. Companies within the Johnson & Johnson Family of Companies market the 1200 mg soft gel vaginal insert in 10 of these 19 countries (Table 6).

Table 6. Countries in which [redacted] markets 1200 mg vaginal [redacted] for the treatment of VVC and date of approval

Country	Year of Approval	Prescription or OTC
Denmark	1982	Prescription
Italy	1984	Prescription
Netherlands	1985	Prescription
Israel	1985	Prescription
Columbia	1985	Prescription
Belgium	1985	OTC
United Kingdom	1986 1991	Prescription OTC
G.D. Luxembourg	1986	OTC
Kuwait	1989	OTC
Ireland	1989	Prescription

(Adapted from the Applicant's Table 3., Vol. 1.1, p. 02-000016)

GYNO-DAKTRIN™ 1 (1200 mg vaginal [redacted] has been marketed in the United Kingdom since July of 1986. This same formulation was approved for OTC use in the U.K. in 1991 and was first marketed OTC (under the trade name Femeron™) in July of 1992. Over the time period of January 1992 to February 1998 the Department of Health Medicines Control Agency in the U.K. reported two patients with adverse drug reactions after using the 1200 mg vaginal [redacted] The reactions were diarrhea and headache in one patient and dizziness and headache in the other patient.

One recent addition to the regulatory history of the 1200 mg soft gel vaginal insert is the approval of an identical product in Canada. On February 5, 1999, McNeil Canada received approval to market an identical 1200 mg soft gel vaginal insert in Canada as an over-the-counter treatment for VVC both with and without the 2% external vulvar cream.

8. Clinical Studies

8.1. Introduction

The Applicant completed two randomized single-blind, phase 3, multi-center studies each enrolling approximately 280 patients. The studies were designed to compare the efficacy and safety of the MONISTAT® DUAL-PAK® (MONISTAT® 1200 mg Soft Gel Vaginal Insert and MONISTAT® (2%miconazole nitrate) External Vulvar Cream) with the approved MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream in patients with vulvovaginal candidiasis. The vaginal insert is administered as a one-time dose and the accompanying external vulvar cream can be used twice daily for up to 7 days. The MONISTAT®7 regimen is administered as one pre-filled applicator nightly for a total of 7 days. The studies compiled data on both the comparative safety and efficacy for the two treatment regimens.

8.2. Indication: Treatment of Vulvovaginal Candidiasis

MO Comment: The MO evaluated a randomly selected sample of 20% of the study population prepared by the Agency's Statistical Reviewer to determine whether the Applicant's assessments of evaluability and outcomes could be accepted for each of the two pivotal trials (96-006 and 97-006). The MO reviewed study eligibility, assessments at RV1 and RV2, reasons for study discontinuation, determination of evaluability/non-evaluability, timing of the RV1 and RV2 assessments, and determination of the overall and therapeutic response categories. Any deviations that

occurred from the protocol-specified criteria and their potential effect on the data were analyzed. The MO found that the methods of evaluation for the two treatment groups were equivalent. The MO was concerned about the Applicant's widening of the protocol specified visit windows and performed an MO efficacy analysis to address this concern. Other than the noted concern regarding the widening of the specified visit windows, the MO accepted the Applicant's evaluability and outcome assessments for both of the pivotal trials. These findings were shared with the Statistical Reviewer, Dr. Cheryl Dixon.

In order to address the MO's concern regarding the Applicant's widening of the protocol specified visit windows and the potential effect this may have on efficacy results, the MO performed an additional efficacy analysis for each of the two pivotal trials. These analyses examined the efficacy results in the subset of evaluable patients who were compliant with the protocol specified visit windows.

APPEARS THIS WAY ON ORIGINAL

8.2.1. Trial #1: Study 96-002 – A Single-Blind Safety and Efficacy Study Comparing a Single Dose (1200 mg) Miconazole Nitrate Vaginal [redacted] to MONISTAT® 7 Vaginal Cream (100 mg Miconazole Nitrate) in the Treatment of Vulvovaginal Candidiasis (VVC)

Objective/Rationale

To determine the safety and efficacy of a vaginal [redacted] containing 1200 mg of miconazole nitrate, administered as a single dose, compared to commercially available MONISTAT® 7 Vaginal Cream (100 mg), administered once daily for 7 days, in the treatment of patients with vulvovaginal candidiasis.

Design

The study was a randomized, single-blind, parallel group, Phase 3, multi-center study of 278 outpatients with documented vulvovaginal candidiasis. The study compared a single dose of the MONISTAT® 1200 mg Soft Gel Vaginal Insert and MONISTAT® External Vulvar Cream (MONISTAT® DUAL PAK®) with the approved 7-day MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream. All medication was self-administered. The study was designed to determine the equivalence of the two products. It was conducted at 13 centers (12 centers within the U.S. and one center in Latin America), each enrolling from 5 to 30 patients. The study took place from October 1996 through May 1997.

Protocol Overview

Population, procedures

Patients were required to meet the following inclusion and exclusion criteria for study participation.

Noteworthy inclusion criteria

- 18 years of age or older
- Use an effective non-barrier method of contraception (including but not limited to oral contraceptives, levonorgestrel implants, IUD, Depo-Provera injections, sterilization of either partner, at least one year post-menopausal, or abstains from sexual intercourse for the duration of the study)
- Agree to use sanitary protection other than tampons in the case of menses during the course of the study
- Reporting or exhibiting at least one positive clinical vulvovaginal sign or symptom from this listing:
    - vulvovaginal itching
    - vulvovaginal burning/irritation
    - vulvar erythema

- vulvar edema
- vulvar excoriation
- vaginal erythema
- vaginal edema

(Discharge information will be collected, but will not be a criterion for inclusion or exclusion of a patient.)

- Papanicolaou smear taken at admission or within 30 days prior (with documentation) as a screening procedure.
- The following laboratory requirements are to be met:
  - positive 10% KOH preparation for yeast
  - negative wet mount result for *Trichomonas vaginalis* and clue cells done at admission
  - BiGGY culture for *Candida* species taken at admission (must be positive for evaluability)
  - test for *Neisseria gonorrhoeae*

Noteworthy exclusion criteria

- Use of any systemic anti-infective or vulvovaginal therapeutic including vaginal or cervical contraceptive devices, vaginal lubricants, foams, jellies, ointments, medicated douches, or feminine sprays within 7 days of admission; or use of water douches within 3 days of admission to avoid false negative KOH preparations and or cultures
- History of sensitivity to the imidazole class of drugs, or any component of the ovule and cream formulation
- Vulvovaginal infection(s) associated with pathogens other than the *Candida* species
- Active genital herpetic lesions at the time of admission
- Presence or treatment of genital condylomata within 30 days of admission
- Has had more than one documented yeast infection within a 2-month period or yeast infections that do not clear up with proper treatment
- Had a papanicolaou smear taken at admission or within 30 days with carcinoma in-situ or worse noted.

MO Comment: The inclusion and exclusion criteria as listed in the protocol are acceptable.

The study involved three patient visits:

- Admission (Day 1 – 1st day of treatment)
- Return Visit 1 (Day 15-19)
- Return Visit 2 (Day 35-43)

At each of the visits patient symptoms, clinical findings, and microbiological investigations were performed. In addition, information