CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-261

MEDICAL REVIEW

OTC MEDICAL OFFICER'S SAFETY UPDATE REVIEW

NDA 21-261
Drug Name: Miconazole Nitrate 200 mg Vaginal Cream
Miconazole Nitrate 2% External Cream
Sponsor: Personal Products Company
Pharmacologic Category – Antifungal
Proposed Indication: To Treat Vaginal Candida albicans Infections
Dosage Form/Route of Administration: Cream/Prefilled Vaginal Applicators and External Digital Application of Cream
Submission Date: 8/3/2000
Review Date: 8/25/00
Reviewer Name: Andrea Leonard-Segal, M.D., M.S.
Project Manager: Daniel Keravich

BACKGROUND:

Personal Products Company is proposing to market a combination pack over-the-counter which will include three 4% miconazole nitrate vaginal cream (200 mg) pre-filled applicators (approved via NDA 20-827) and a 9 g tube of 2% miconazole nitrate external cream. The 2% external cream is already approved for the external relief of symptoms associated with a vaginal yeast infection and is indicated for use concurrently with 2% intravaginal miconazole cream (100 mg in each applicator) for 7 days or 200 mg suppositories for 3 days.

MATERIAL REVIEWED:

This review is a summary of the:

1. **Periodic Annual Report** for NDA 17-450 Monistat® 7 Vaginal Cream for the dates January 1 – December 31, 1999

2. **Quarterly Reports** for NDA 20-827 Monistat® 3 Vaginal Cream
   a. March 1, 2000 – May 31, 2000
   b. December 1, 1999 – February 29, 2000
   c. September 1, 1999 – November 30, 1999
   d. June 1, 1999 – August 31, 1999
   e. March 1, 1999 – May 31, 1999
   f. December 1, 1998 – February 28, 1999

3. **Global Safety Update** – Janssen Research Foundation Periodic Safety Update Report (#R14889), October 5, 1999

1. Periodic Annual Report for Monistat® 7 Vaginal Cream

There were no serious adverse events reported from January 1, 1999 through December 31, 1999. There were 949 non-serious adverse event reports from spontaneous domestic sources received by the sponsor during this reporting period that detailed 1023 adverse

reactions. **Table 1** categorizes the non-serious adverse reactions according to body system.

Table 1. Non-serious reactions for Monistat® 7 Vaginal Cream

Body System	Number (#) of Adverse Reactions
Reproductive System and Breast Disorders (female genital disorder, vaginal discharge, vaginal hemorrhage, vaginal pain, vulval edema, vulvovaginal discomfort, penile pain, penile rash)	742
Skin and Subcutaneous Tissue Disorders (erythema, genital itching, generalized rash)	131
General disorders (application site reaction, drug ineffective, nonspecific reaction, pyrexia)	92
Gastrointestinal disorders (abdominal pain, nausea, vomiting, bitter taste in mouth)	34
Nervous System Disorders (headache, dizziness, nervousness)	11
Musculoskeletal (back pain)	7
Renal and Urinary Disorders	3
Cardiac Disorders (tachycardia)	1
Immune Disorder (allergic reaction)	1
Accidental Exposure	1

Two men developed a penile rash and 1 developed penile burning after exposure to the drug during sexual intercourse.

15-Day Reports

Twenty-two 15-Day reports (domestic and foreign) were included in the annual report for Monistat® 7 Vaginal Cream. However, the indications, formulations, and routes of administration in these cases varied (intravenous, intrathecal, oral table, oral gel, or vaginal cream).

1. Five reports were of parenteral or intrathecal miconazole administration. One heart transplant patient may have developed *arrythmias* secondary to miconazole administration. Another patient developed a *rash* possibly attributable to miconazole. Based on the information provided in the 3 remaining reports, the medical conditions described could not be reliably attributed to miconazole.
2. One patient who was taking [redacted] formulation, delivery route, and dose unavailable) and an anticoagulant *died*, but the report did not provide adequate information to be able to attribute the death to miconazole.
4. One diabetic consumer developed *severe external vaginal swelling* after using Monistat 7 Vaginal Cream.

5. One pregnant woman in the first trimester had a spontaneous abortion immediately following use of intravaginal miconazole.
6. One patient developed a *rash* after taking [redacted] tablets for 1 week.
7. One woman on with a stable INR on warfarin developed *bruising* while using [redacted] oral gel for thrush.
8. The remaining reports (oral gel, vaginal cream) were confounded, provided inadequate information, or demonstrated inappropriate use of a miconazole preparation (i.e., one case of too much oral gel in a 1 month old infant).

2. Quarterly Reports for Monistat® 3 Vaginal Cream

There were no serious adverse events reported during any of the quarters considered in this review. There were a total of 993 non-serious reports describing 1129 adverse reactions. **Table 2** categorizes the non-serious reports according to body system.

Table 2. Non-serious reactions for Monistat® 3 Vaginal Cream.

Body System	# of Adverse Reactions
Reproductive (vulvo-vaginal discomfort – burning, bloody discharge, non-bloody discharge, vulvo-vaginal edema, penile pain)	901
Skin (rash, genital itching, generalized itching, erythema)	134
General Disorder (ineffective, application site reaction, nonspecific reaction)	43
Gastrointestinal (abdominal pain, nausea, diarrhea)	39
Body as Whole (headache, sore feeling in mouth, sore eye)	4
Nervous System (lightheadedness, dizziness, shakiness)	3
Musculoskeletal (back pain,	4
Urinary (urinary irritation)	1

Many reactions (burning, genital itching, discharge, edema, erythema, or bloody discharge) could have been secondary either to the primary condition and/or the treatment. One woman reported vaginal blisters and one a "vaginal bump."

Thirty-four people described a generalized rash or generalized itching, which could have been an allergic reaction to the medication.

One man developed penile burning and redness following exposure to Monistat® 3 during sexual intercourse.

Comment: Monistat® 7 and 3 are for vaginal use. The 4 reports of adverse reactions in men can probably be attributed to exposure to miconazole during sexual intercourse with women who were using the product. The newer Monistat® 7 labeling warns not to use this product during sexual intercourse. This warning should be incorporated into the Monistat® 3 combination product.

3. [redacted] **Safety Update Report (R14889)**

This report is the third safety update on miconazole gynecologic formulations (cream, ovules, capsules) compiled for regulatory authorities. The report states that the material was complied in accordance with the International Conference on Harmonization (ICH) Guideline *Periodic Safety Update Reports for Marketed Drugs*. It summarizes the safety data received as assessed by the [redacted] department at the from worldwide sources from August 16, 1996 through August 14, 1999. The attribution estimate of the [redacted] drug involved is expressed as either:

1. Not related: An adverse event that is unrelated to the use of the drug.
2. Doubtful: An adverse event for which an alternative explanation is more likely (e.g., concomitant drug, concomitant disease) and/or the relationship in time suggests that a causal relationship is unlikely.
3. Possible: An adverse event that might be due to the use of the drug. An alternative explanation (e.g., concomitant drug or disease) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
4. Probable: An adverse event that might be due to the use of the drug. An alternative explanation is less likely. The relationship in time is suggestive (e.g., confirmed by de-challenge).
5. Very likely: An adverse event that is listed as a possible adverse reaction and cannot be reasonable explained by an alternative explanation. The relationship in time is very suggestive (e.g., it is confirmed by de-challenge and re-challenge).

According to the ICH guidelines, cases for which the causality has been scored lower than "possible" (that is, "not related" or "doubtful') by both reported and [redacted] are excluded from the periodic update safety report. Miconazole vaginal cream [redacted] was first registered in Belgium in August 1971 and there were 2 earlier safety updates on miconazole. There were no regulatory authority actions taken for safety reasons during the period covered by this report.

During the period covered by this periodic safety report a total of 80 initial reports were received. In 78 cases, the report states that attribution estimate was at least "possible" and only these cases were discussed in the report. Two of these cases were derived from the literature, 2 from a health authority, and 16 were spontaneous. A total of 58 medically unconfirmed spontaneous reports from consumers or non-health care professionals were received during the time frame of the report.

Table 3 lists the frequency of adverse events by body system in the 20 patient reports derived from non-consumer or non-health care professional sources.

Table 3. Adverse events for miconazole for non-consumer and causal related cases.

Reaction	# of Adverse Events
Application Site Reaction	5
Allergic Reaction	1
Anaphylaxis	1
Drug interaction	3
Lack of efficacy	1
Fever	1
Pain (general)	1
Mucosal burning	2
Skin burning	1
Headache	2
Vertigo	1
Abortion	1
Abdominal pain	1
Nausea	1
Bruise	1
Gingival bleeding	1
Hemorrhage	1
Nosebleed	1
Prothrombin time prolonged	4
Purpura	1
Sleepiness	1
Burning feeling in vagina	1
Vulvovaginitis	1
Pruritis vulvae	1
Urticaria	1
Vaginal itching	2

There were 3 serious adverse events, an anaphylactic reaction and a spontaneous fetal abortion.

1. The patient with an *anaphylactic reaction* was a 33-year old woman with a history of atopy, asthma and unspecified allergy. She developed *itching* and a generalized *rash* within a few hours of the miconazole vaginal suppository application. As the reaction progressed, she developed a swollen throat and breathing difficulties. She was hospitalized and recovered within 24 hours with epinephrine, corticosteroid and antihistamine treatment.
2. A 28-year old pregnant woman in her first trimester was prescribed bromopride (as required) and folate. She used miconazole vaginal cream once at 12 weeks of pregnancy. After the first application, there was extravasation of vaginal secretion. She complained of a stomachache and was switched from folic acid to vitamins,

minerals, calcium gluconate and calcium lactobromic by her physician. Three days later, the patient experienced *abdominal pain, hemorrhage*, and a *spontaneous abortion*. A week later she also experienced *headache* and *sleepiness*.

3. The patient with *purpura* was a 73-year old diabetic woman treated with miconazole and intraconazole for vaginitis. Other medications were metformin, [redacted] Biopsy results reported showed a leucocytoclastic vasculitis. The reaction abated after discontinuation of miconazole and itraconazole.

Comment: This case is confounded and was not listed by the sponsor as serious..

There were 4 cases of probable or possible *drug interaction*. None were considered to be serious. Three involved concomitant use of acencoumarol and one involved warfarin resulting in a *prolonged prothrombin time*.

1. A 72-year old woman was on several oral medications (simvastatin, [redacted] levothyroxine, bisoprolol) and triamcinolone ointment. An increased INR was noted 6 days after completion of a 3-day course of 400 mg miconazole vaginal capsules.
2. A 61-year old woman with a history of rheumatic fever and atrial fibrillation used miconazole 400 mg vaginal capsules for 3 days and was on several other medications [redacted] verapamil, enalapril, [redacted] digoxin, urea ointment). An increase in the INR was noted 1 day after discontinuation of miconazole treatment.
3. A 73-year old woman used miconazole vaginal cream for an undetermined duration of time. This patient had recently undergone coronary artery bypass surgery and an aortic valve replacement and was also on simvastatin. It is unknown whether she had already reached a stable anticoagulant regimen.
4. One patient was using vaginal miconazole for 2 days (strength unknown) and took warfarin concomitantly. She developed an *increased prothrombin time, bruising, gingival bleeding*, and a *nosebleed*. She remembered a similar episode after having used clotrimazole vaginal suppositories.

Pregnancy Data

The sponsor states that known pregnancy exposures to miconazole are accumulated in the [redacted] Pregnancy Database Application. This database centralizes information on the offspring following such exposure, regardless of whether the outcome of the pregnancy is normal or abnormal and without regard to a possible causal relationship. It covers both retrospective reports on pregnancies and prospective observations on pregnant patients.

In the cumulative database of vaginal use of miconazole there are 3 reports of congenital abnormalities. One mother had conceived the day after completing a 7-day course of miconazole cream. One mother had used miconazole vaginal cream during the first trimester of her pregnancy. One, HIV positive mother had received didanosine 400 mg/day and zidovudine 500 mg/day during her second trimester. In the third trimester she received lamivudin 300 gm/day and zidovudine 500 mg/day. She took 15 mg

calcium folinate 3 times/week, and used econazole and miconazole ovules for 6 days. In one case, a 31-year old woman used nystatin suppositories and miconazole vaginal cream during her pregnancy (trimester unknown). She also took vitamins and minerals (not otherwise specified). Her baby had a "persistent fetal circulation" that was classified by the sponsor as a neonatal abnormality.

The sponsor notes that the small number of cases reported in contrast to patient exposure is not suggestive of a teratogenic effect, but that given the limited data available of use in pregnant women, the current warnings against use of intravaginal miconazole in pregnant and nursing women should be continued.

No new relevant safety information is available for children, the elderly and organ-impaired individuals, or for effects of long-term treatment, or in studies of miconazole during the period reviewed.

Table 4 summarizes the listing of reports of medically unconfirmed spontaneous reports from consumers or non-health care professionals in 58 people.

Table 4. Medically Unconfirmed Spontaneous Reports

Reaction	# of Reports
Vaginal burning	50
Itching	4
Rash	3
Hives	2
Vulvar redness (in 5 month old baby)	1
Uterine contractions (non-pregnant woman)	1
Chest heaviness	1

The patient with chest heaviness was a 38-year old woman with esophageal spasm on cisapride and omeprazole.

Discussion

The data in these reports indicates that miconazole vaginal cream is safe when used as directed. The product labeling should retain warnings about use in pregnancy and nursing because there is no data presented that proves that is safe when used during these conditions. Side effects in men may be avoided with the label warning against having sexual intercourse when using this product. The complaints in men occurred after sexual exposure to women who were using the product. Vaginal burning and itching are common, but not serious. The current labeling adequately informs of the possibility of allergic reaction. There were very few serious allergic reactions reported.

Women on warfarin anticoagulants may be at risk for bleeding when they use miconazole vaginal preparations and should be warned as such. There were several post-marketing reports of women who may have had a drug interaction between their warfarin anticoagulant and miconazole. Although no more than 1.3% of miconazole is absorbed

vaginally, the drug, an imidazole derivative, inhibits the microsomal cytochrome P_{450} system.[1] It is known to enhance the antiocagulant effect of warfarin.[2]

Conclusion:
The labeling should warn consumers who take a warfarin anticoagulant to check with their physician before using the Monistat® 3 combination cream product. This warning should appear on the label for all of the miconazole vaginal products, as well.

The current warning against product use if a woman is pregnant and nursing women should remain.

The warning not to use this product during sexual intercourse may eliminate side effects in men.

Current allergy warnings are adequate.

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References:

1. Gilman AG, Rall, TW, Nies, AS, Taylor P: The Pharmacological Basis of Therapeutics, McGraw Hill, 1990, pp 1170-1171, 1177.

2. Moreau D: Physician's Drug Handbook, Springhouse Corporation, 1995, pp 668-669.