CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-308/S-009

Name: Monistat 1 Combination Pack
(1200 mg Miconazole Nitrate Vaginal Insert
and 2% Miconazole Nitrate Cream)

Sponsor: Personal Products Company

Approval Date: October 1, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-308/S-009

Personal Products Company
Attention: Terry Glass, Esq.
Director, Regulatory Affairs
199 Grandview Road
Room SF101
Skillman, NJ 08558

Dear Ms. Glass:

Please refer to your supplemental new drug application dated December 2, 2003, received December 3, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monistat 1 Combination Pack (1200 mg miconazole nitrate vaginal insert and 2 % miconazole nitrate cream).

We acknowledge receipt of your submissions dated December 12, 2003, January 16, January 20, February 13, August 11, August 17, August 18 and September 7, 2004.

This supplemental new drug application proposes to change the labeling instructions for Monistat 1 Combination Pack (miconazole nitrate) to allow for daytime administration of the drug product, in addition to the current bedtime administration, to treat vulvovaginal candidiasis.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the carton and Drug Facts labeling submitted September 7, 2004, and text for the consumer information leaflet submitted August 18, 2004), and must be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-308/S-009." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Leah Cutter, Ph.D., Regulatory Project Manager, at (301) 827-2248.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
10/1/04 10:11:10 AM
NDA 21-308/S-009

Charles Ganley
10/1/04 11:35:30 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

LABELING

Brand	- Monistat	**File name**	- XXXXXX_M1Day_Night	**Design Agency Reference**	- AGT*seven
Category	- Vaginal Anti Fungal	**Dieline No.**	- 337387	**Project Name**	- Cooling Updates
Product Variant	- Combo Pack	**Barcode No.**	- XXXXXX	**Artwork program**	- Ill. 10
Component Type	- XXXXXX	**AGT*seven Job No.**	- 60694/2314	**Lead Mktg. Country**	- USA
Consumer Unit Contents	- 1	**Formulation No.**	- n/a	**Sales Region**	- North America
Copy & Graphics Number	- XXXXXX	**Printer**	- PCI Services	**Manufacturing Site**	- PSGA
Version#	- XXXXXX/1	**No. of Colours**	- 6	**Library**	- Local Market Artwork
Date	- 8/17/04	**Print Method**	- Offset	**Keywords (Market)**	- XXXXXX, PC XXXX

FDA STANDARD SIZES for Drug Facts
12 point Helvetica Bold Italic Title
10 point Helvetica Bold Italic Title (2nd column)
8 point Helvetica Bold Italic Headings
8 point Helvetica Condensed Med "Continued"
6 point Helvetica Bold Subheads
6 point Helvetica Regular Text
6.5 point Leading

2.5 point box hairline
2.5 point hairline
0.5 point hairline
5 point ITC Zapf Dingbats Bullet

Manufactured Gold is needed for rules
try to create with
(109 / 100%) – (Cool Grey 18%) – (226 / 8%)

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

TAMPER EVIDENT UNIT
DO NOT USE IF **PRINTED** SEALED POUCH OR SEALED VAGINAL INSERT BLISTER IS TORN, OPEN OR INCOMPLETELY SEALED

Distributed by:
Personal Products Company
Division of McNeil-PPC, Inc., Skillman, NJ 08558
MADE IN U.S.A. ©McNeil-PPC, Inc. 2003
702-30-401-2
718605
Covered under patent number 5,514,698

FPO
3 8004-5411-00 0

? If you have any questions or comments, please call 1-877-MONISTAT (1-877-666-4782) or visit our website at www.monistat.com

ONE TREATMENT
OVULE® Insert
plus External Cream
for Itch Relief

DAY or NIGHT
STAYS IN PLACE

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

? If you have any questions or comments, please call 1-877-MONISTAT (1-877-666-4782) or visit our website at www.monistat.com

NDC 62341-5411-0

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)

CLINICALLY PROVEN ORTHO

VAGINAL ANTIFUNGAL
CURES MOST VAGINAL YEAST INFECTIONS AND
RELIEVES ASSOCIATED EXTERNAL ITCHING AND IRRITATION

1 OVULE® Insert with Applicator
plus External Cream

ORTHO

Net Wt. 1 OVULE® Insert
+
0.32 oz. (9g) Tube

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) and Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

LOCATION OF LOT#
AND EXPIRATION DATE

bar code area

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

1 - DAY TREATMENT CURES MOST VAGINAL YEAST INFECTIONS

Drug Facts

Active ingredients — **Purpose**
Miconazole nitrate 1200 mg (in vaginal insert)..... Vaginal antifungal
Miconazole nitrate 2% (external cream)..... Vaginal antifungal

Uses
- treats vaginal yeast infections
- relieves external itching and irritation due to a vaginal yeast infection

Warnings

For vaginal use only

Do not use if you have never had a vaginal yeast infection diagnosed by a doctor

Ask a doctor before use if you have
- **vaginal itching and discomfort for the first time**
- **lower abdominal, back or shoulder pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge. You may have a more serious condition.**
- vaginal yeast infections often (such as once a month or 3 in 6 months). You could be pregnant or have a serious underlying medical cause for your symptoms, including diabetes or a weakened immune system.
- been exposed to the human immunodeficiency virus (HIV) that causes AIDS

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine warfarin, because bleeding or bruising may occur

When using this product
- do not use tampons, douches, spermicides or other vaginal products. Condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases (STDs).
- do not have vaginal intercourse
- mild increase in vaginal burning, itching or irritation may occur

Drug Facts (continued)

Stop use and ask a doctor if
- **symptoms do not get better in 3 days**
- **symptoms last more than 7 days**
- **you get a rash or hives, abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge**

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions
- before using this product read the enclosed consumer information leaflet for complete directions and information
- adults and children 12 years of age and over:
  - **vaginal insert:** with the applicator place the vaginal insert into the vagina. Throw applicator away after use.
  - **external cream:** squeeze a small amount of cream onto your fingertip. Apply the cream onto the itchy, irritated skin outside the vagina. Use 2 times daily for up to 7 days, as needed.
- children under 12 years of age: ask a doctor

Other information
- do not use if **printed** sealed pouch is torn, open or incompletely sealed
- do not use if seal over tube opening has been punctured or embossed design ▽ is not visible
- do not purchase if carton is open
- store at 20°-25°C (68°-77°F)
- this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days.

Inactive ingredients
- vaginal insert: gelatin, glycerin, lecithin, mineral oil, titanium dioxide, white petrolatum
- external cream: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol

Questions? **If you have any questions or comments, please call 1-877-666-4782**

bar code area

Consumer Information Leaflet

624-10-403-3

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)

VAGINAL ANTIFUNGAL

Cures Most Vaginal Yeast Infections

and Relieves Associated External Itching and Irritation

Why should I use MONISTAT® 1 Combination Pack?

MONISTAT® 1 Combination Pack contains a 1-dose OVULE® Insert that cures most vaginal yeast infections, plus an external cream that can be used for relief of itching and irritation on the skin outside the vagina (vulva) due to a yeast infection. ***Do not use MONISTAT® 1 Combination Pack if this is the first time you have vaginal discharge, itching, burning and discomfort. See your doctor or health professional first to find out the cause of your symptoms.*** If a doctor has told you in the past that you had a vaginal yeast infection and you have the same symptoms now (such as vaginal discharge, itching or burning), then MONISTAT® 1 Combination Pack may work for you.

What is a vaginal yeast infection?

A vaginal yeast infection is a common condition caused by an overgrowth of yeast (Candida) that may normally live in the vagina. Your doctor may call this infection "monilia" or "candidiasis." Some women may have a yeast infection on the skin outside of the vagina (vulva) at the same time that they have a vaginal infection.

Who can get a vaginal yeast infection?

You can get a vaginal yeast infection at any age. It is most common during the childbearing years. Women who are pregnant or diabetic, taking antibiotics, birth control pills or steroids, or who have a weakened immune system are more likely to get repeated yeast infections that may not clear up easily with proper treatment.

Some medical conditions can weaken the body's normal ability to fight infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV – the virus that causes AIDS). The HIV virus causes the body to be more likely to get infections, including vaginal yeast infections that may not clear up easily with proper treatment. If you may have been exposed to HIV and get repeated vaginal yeast infections, you should see your doctor right away. For more information on HIV infection, please contact your doctor or the CDC National AIDS HOTLINE. The CDC phone numbers are: 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

How can I tell if I have a vaginal yeast infection?

When you have a vaginal yeast infection, you may have one or more of the following symptoms:

- vaginal itching
- vaginal discharge that may be thick, white, and lumpy like cottage cheese
- vaginal soreness, irritation, or burning
- rash or redness on the skin outside the vagina (vulva)
- burning on urination
- painful vaginal intercourse (sex)

Note: Vaginal yeast infections do NOT cause fever, chills, lower abdominal, back or shoulder pain, foul-smelling vaginal discharge, or a missed period. These may be signs of a sexually transmitted disease (STD) or a tubal pregnancy. If you have these symptoms, call your doctor right away.

What are other causes of a vaginal discharge?

It is normal to have a small amount of vaginal discharge at certain times of the month. This normal discharge may be clear or slightly white and does not cause itching, pain or a foul odor.

The most common cause of an abnormal vaginal discharge is an infection. These infections include bacterial vaginosis (BV), trichomoniasis (Trich), gonorrhea (GC) and/or chlamydia. All of these may be transmitted sexually and are called sexually transmitted diseases (STDs). If you have more questions about sexually transmitted diseases (STDs) call the CDC STD Hotline at 1-800-227-8922.

Although many of the infections mentioned above can cause symptoms similar to a vaginal yeast infection (vaginal discharge, irritation and itching), their diagnosis must be made by a doctor so that proper treatment can be given.

If these infections are not properly treated or if proper treatment is delayed, serious problems, such as pelvic inflammatory disease (PID) may result, which may prevent you from having children in the future. If you are pregnant and do not get the proper treatment, the infection may be passed to your baby before or during delivery and may cause your baby to have permanent damage. If you have multiple sex partners or a new sex partner, you should also ask a doctor before use to make sure you do not have an STD.

Why do women get repeated vaginal yeast infections?

Women may get repeated vaginal yeast infections that may not clear up easily with proper treatment. Listed below are some of the causes of repeated yeast infections:

- **hormonal changes** occurring a few days before the monthly period
- **use of antibiotics**
- **use of some birth control pills**
- **pregnancy**
- **diabetes ("sugar" or "high blood sugar")**
- **clothing** – wearing tight layers or moist clothing in the genital area
- **weakened immune system** – some drugs (such as chemotherapy or steroids) and medical conditions can weaken the body's normal ability to fight infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV – the virus that causes AIDS). Infection with HIV causes the person to be more likely to get infections, including vaginal yeast infections.

If you get vaginal yeast infections often (such as once a month or 3 in 6 months), you should talk to a doctor.

Are vaginal yeast infections sexually transmitted?

Vaginal yeast infections are usually not spread by having intercourse (sex). However, if your partner has a rash, itching or discomfort in his genital area, he should contact a doctor to find out the cause of his symptoms and tell the doctor that you are treating your vaginal yeast infection with MONISTAT® 1 Combination Pack.

How can I prevent repeated vaginal yeast infections?

To lower your chances of getting another yeast infection:

- **Try to keep the genital area cool and dry.** Yeast grow well in warm, moist areas. The following suggestions may be helpful:

(1) Wear cotton underwear and loose-fitting clothes.

(2) Change out of damp clothes or a wet bathing suit as soon as possible.

(3) If you use minipads when you are not having a menstrual period, change the minipads often.

- **Talk with your doctor about any drugs you are now taking.** You are more likely to get a vaginal yeast infection if you are taking certain drugs such as antibiotics, steroids, or birth control pills. Do not stop taking these drugs without first asking your doctor. A doctor may need to see you to make sure that you do not have other medical conditions such as diabetes or a weakened immune system.

Can I use MONISTAT® 1 Combination Pack during my menstrual period?

Yes, this product can be used during your menstrual period. In fact, many women get vaginal yeast infections just before their period because of hormonal changes. Using MONISTAT® 1 Combination Pack during your period will not affect how well this product works. If you have started treatment and your period occurs, you should complete the full course of treatment.

Do not use tampons while using this product, because tampons may remove some of the drug from the vagina. Use deodorant-free sanitary napkins or pads instead, and change them often.

Can I use other vaginal products with MONISTAT® 1 Combination Pack?

This drug should **not** be used with other vaginal products.

- Douches and tampons may remove some of the OVULE® Insert from the vagina.
- Spermicides may interfere with MONISTAT® 1 Combination Pack.
- Condoms and diaphragms may be damaged by this product and fail to prevent pregnancy or sexually transmitted diseases (STDs).

Brand	- Monistat	**File name**	- Mon1 non prefilled ComboInsert	**Design Agency Reference**	- SEVEN
Category	- Vaginal Antifungal	**Dieline No.**	- n/a	**Project Name**	- Daytime
Product Variant	- non-Prefilled (Ovual Insert) Combination	**Barcode No.** (+ BWR & Mag)	- n/a	**Artwork program**	- Illustrator 8.0
Component Type	- Insert	**Seven Job No.**	- 6069/2314	**Lead Mktg. Country**	- USA
Consumer Unit Contents	-	**Formulation No.**	- n/a	**Sales Region**	- North America
Copy & Graphics Number	- XXXXXX	**Printer**	- PCI Triline	**Manufacturing Site**	- PSGA
Version#	- 2	**No. of Colours**	- 2	**Library**	- Local Market Artwork
Date	- 8/17/04	**Print Method**	- offset	**Keywords (Market)**	- XXXXXX

Johnson & Johnson
199 Grandview Road
Skillman, NJ 08558-9418
908-874-1666 (Consumer Graphics Dept. Fax)

¥ This proof indicates approximate color only!
¥ All colors print 100% unless otherwise indicated.
¥ All structure and holding lines do not print unless otherwise indicated.
¥ This is prepared as a color digital mechanical, no traps have been made.
¥ All trapping is the responsibility of the engraver and/or separator and/or printer.

ARTWORK SPECIFICS

Colors: 2
Note: All colors for reference only, printer to use pre-approved color drawdowns when printing.

PANTONE® 300

PANTONE® Cl Gy 10

Fonts:
Optima / MathPi / Helv. Condensed
Helv. Neue / Helv. Neue Condensed
Helv. Neue Extended, Helv. Condensed-Italic, Helv. Roman

Consumer
Graphics Manager: Bridgette Motley
Phone: 908.874.2736

How can I get the best results when treating my infection?

- Use the OVULE® Insert, even during your menstrual period.
- Use the tube of cream externally only while symptoms are present. If you have symptoms (such as itching and irritation) on the skin outside the vagina (vulva), apply the cream externally 2 times a day, up to a total of 7 days, as needed.
- Dry the genital area thoroughly after a shower, bath or swim. Change out of a wet bathing suit or damp clothes as soon as possible. A dry area is less likely to lead to the overgrowth of yeast.
- Wear cotton underwear and loose-fitting clothes.
- Wipe from front to back after a bowel movement or after urination.
- Do not douche, because douching may wash the drug out of the vagina.
- Do not use tampons, because they remove some of the drug from the vagina. Use deodorant-free sanitary napkins or pads as needed.
- Do not use spermicides, as they may interfere with MONISTAT® 1 Combination Pack.
- Do not have vaginal intercourse while using MONISTAT® 1 Combination Pack.
- Do not scratch the skin outside the vagina. Scratching can cause more irritation and can spread the infection.
- **Tell your doctor about any drugs you are now taking**. Certain drugs such as antibiotics, steroids, and birth control pills, may make it more likely for you to get a vaginal yeast infection. If you are taking any of these drugs do not stop taking them without first asking a doctor.
- If you have any other medical questions or concerns about vaginal yeast infections, call your doctor.

What warnings should I know about when using MONISTAT® 1 Combination Pack?

For vaginal use only.

Do not use if you have never had a vaginal yeast infection diagnosed by a doctor.

Ask a doctor before use if you have:

- **vaginal itching and discomfort for the first time. You may need a different treatment.**
- **lower abdominal, back or shoulder pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge. You could have a more serious condition.**
- vaginal yeast infections often (such as once a month or 3 in 6 months). You could be pregnant or have a serious underlying medical cause for your symptoms, including diabetes or a weakened immune system.
- been exposed to the human immunodeficiency virus (HIV) that causes AIDS.

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine, warfarin (coumadin), because bleeding or bruising may occur.

When using this product:

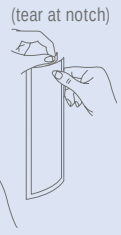
- do not use tampons, douches, spermicides, or other vaginal products. Condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases (STDs).
- do not have vaginal intercourse
- mild increase in vaginal burning, itching or irritation may occur

6-DIGIT BAR CODE 1/2" HEIGHT

How Should I Use MONISTAT® 1 Combination Pack ?

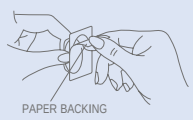
This product is for adults and children 12 years of age and over. For children under 12 years, ask a doctor.

Directions for using the Applicator and the OVULE® Insert :



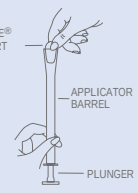
1 Open pouch and remove contents. (see picture).
KEEP CONTENTS DRY BEFORE USE.

2 Separate the paper backing from blister pack by peeling back the cover from the corner. (see picture).

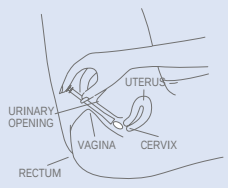


3 Place the OVULE® Insert firmly into the top (wider end) of the applicator so it will not fall out.

4 Hold the Applicator containing the OVULE® Insert by the opposite end from where the OVULE® Insert is located.



5 Gently insert the applicator into the vagina as far as it will go comfortably. This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent, as shown in the picture.



6 With one hand holding the barrel, use the other hand to push the plunger all the way in to place the OVULE® Insert as far back in the vagina as possible. Then remove both parts of the applicator from the vagina.

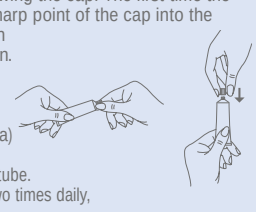
7 Throw away applicator after use. Do not flush in toilet.

You may want to use deodorant-free pads or pantyshields to protect your clothing during the time that you are using MONISTAT® 1 Combination Pack. This is because the OVULE® Insert can leak or you may get some discharge. **Do not use tampons, douches, spermicides, condoms or diaphragms** until after you have completed the treatment and your symptoms are gone.

Directions for using the External Vulvar Cream

Use the cream twice daily, for up to 7 days as needed.

1. Open the tube by unscrewing the cap. The first time the tube is opened, press the sharp point of the cap into the sealed end of the tube. Push down firmly until the seal is open.
2. Squeeze a small amount of cream onto your fingertip.
3. Apply the cream onto the skin outside the vagina (vulva) that itches and is irritated.
4. Screw the cap back on the tube.
5. Repeat steps 2 – 4, up to two times daily, as needed.



Stop use and ask your doctor if:

- **symptoms do not get better in 3 days**
- **symptoms last more than 7 days**
- **you get a rash or hives, abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge.**

These may be signs that this product is not working, or you may have a more serious condition or an allergic reaction.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

What side effects may occur with MONISTAT® 1 Combination Pack?

A mild increase in vaginal burning, itching, or irritation may occur when the OVULE® Insert is inserted. Abdominal cramping has also been reported.

Stop using MONISTAT®1 Combination Pack and consult your doctor if you have abdominal pain, hives, skin rash, or if you have severe vaginal burning, itching, or irritation or swelling.

What should I do if I have questions about MONISTAT® 1 Combination Pack?

Questions of a medical nature should be taken up with your doctor. If you have any other questions or need more information on this product, call our toll-free number. Call between 8:00 AM and 5:00 PM Eastern time, Monday through Friday. A health care specialist will gladly answer your questions. Our toll-free number is 1-877-MONISTAT (1-877-666-4782).

Other Information:

- **TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed**.
- do not use if tube seal has been punctured or embossed design ▽ symbol is not visible.
- store at 20° – 25° C (68° – 77° F)
- this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days.

Active ingredients: OVULE® Insert: miconazole nitrate, 1200 mg. External Vulvar Cream – miconazole nitrate, 2%.

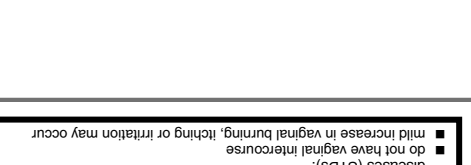
Inactive ingredients: OVULE® Insert: gelatin, glycerin, lecithin, mineral oil, titanium dioxide, white petrolatum. External Vulvar Cream: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol.

Distributed by:
Personal Products Company
Division of McNeil-PPC, Inc.
Skillman, NJ 08558

624-10-403-3

ONE TREATMENT
OVULE® Insert Prefilled Applicator
plus External Cream
for Itch Relief

DAY OR NIGHT
STAYS IN PLACE



MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)

VAGINAL ANTIFUNGAL

? If you have any questions or comments, please call 1-877-MONISTAT (1-877-666-4782) or visit our website at www.monistat.com

NDC 62341-5411-2

CONVENIENT PREFILLED APPLICATOR

MONISTAT®
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)

1

CLINICALLY PROVEN
ORTHO

VAGINAL ANTIFUNGAL

CURES MOST VAGINAL YEAST INFECTIONS AND
RELIEVES ASSOCIATED EXTERNAL ITCHING AND IRRITATION

1 OVULE® Insert Prefilled Applicator
plus External Cream

ORTHO

Net Wt. 1 OVULE® Insert
+
0.32 oz. (9g) Tube

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) and Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

LOCATION OF LOT#
AND EXPIRATION DATE

MONISTAT® 1
COMBINATION PACK
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VAGINAL ANTIFUNGAL

? If you have any questions or comments, please call 1-877-MONISTAT (1-877-666-4782) or visit our website at www.monistat.com

3 80041-5411-00 0

FPO

Distributed by:
Personal Products Company
Division of McNeil-PPC, Inc., Skillman, NJ 08558
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702-30-4017-2
718606
Covered under patent number 5,514,698

TAMPER EVIDENT UNIT
DO NOT USE IF
PRINTED SEALED
POUCH IS TORN, OPEN
OR INCOMPLETELY
SEALED

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) and Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

1 - DAY TREATMENT CURES MOST VAGINAL YEAST INFECTIONS

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) and Miconazole Nitrate Cream (2%)
VAGINAL ANTIFUNGAL

Drug Facts

Active ingredients	Purpose
Miconazole nitrate 1200 mg (in vaginal insert)	Vaginal antifungal
Miconazole nitrate 2% (external cream)	Vaginal antifungal

Uses
- treats vaginal yeast infections
- relieves external itching and irritation due to a vaginal yeast infection

Warnings
For vaginal use only

Do not use if you have never had a vaginal yeast infection diagnosed by a doctor

Ask a doctor before use if you have
- **vaginal itching and discomfort for the first time**
- **lower abdominal, back or shoulder pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge. You may have a more serious condition.**
- vaginal yeast infections often (such as once a month or 3 in 6 months). You could be pregnant or have a serious underlying medical cause for your symptoms, including diabetes or a weakened immune system.
- been exposed to the human immunodeficiency virus (HIV) that causes AIDS

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine warfarin, because bleeding or bruising may occur

When using this product
- do not use tampons, douches, spermicides or other vaginal products. Condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases (STDs).
- do not have vaginal intercourse
- mild increase in vaginal burning, itching or irritation may occur ➡

Stop use and ask a doctor if
- **symptoms do not get better in 3 days**
- **symptoms last more than 7 days**
- **you get a rash or hives, abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge**

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Drug Facts (continued)

Directions
- before using this product read the enclosed consumer information leaflet for complete directions and information
- adults and children 12 years of age and over:
  - **vaginal insert:** with the applicator place the vaginal insert into the vagina. Throw applicator away after use.
  - **external cream:** squeeze a small amount of cream onto your fingertip. Apply the cream onto the itchy, irritated skin outside the vagina. Use 2 times daily for up to 7 days, as needed.
- children under 12 years of age: ask a doctor

Other information
- do not use if **printed** sealed pouch is torn, open or incompletely sealed
- do not use if seal over tube opening has been punctured or embossed design ⌵ is not visible
- do not purchase if carton is open
- store at 20°-25°C (68°-77°F)
- this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days.

Inactive ingredients
- vaginal insert: gelatin, glycerin, lecithin, mineral oil, titanium dioxide, white petrolatum
- external cream: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol

Questions? If you have any questions or comments, please call 1-877-666-4782

Brand	- Monistat	**File name**	- XXXXXX_M1Combo_prefill	**Design Agency Reference**	- **AGT•seven**
Category	- Vaginal Anti Fungal	**Dieline No.**	- 33738R7	**Project Name**	- Cooling Updates
Product Variant	- Combo Pack	**Barcode No.**	- XXXXXX	**Artwork program**	- Ill. 10
Component Type	- XXXXXX	**AGT•seven Job No.**	- 60694/2314	**Lead Mktg. Country**	- USA
Consumer Unit Contents	- 1	**Formulation No.**	- n/a	**Sales Region**	- North America
Copy & Graphics Number	- XXXXXX	**Printer**	- PCI Services	**Manufacturing Site**	- PSGA
Version#	- XXXXXX/1	**No. of Colours**	- 6	**Library**	- Local Market Artwork
Date	- 8/17/04	**Print Method**	- Offset	**Keywords (Market)**	- XXXXXX, PC XXXX

JOHNSON & JOHNSON
199 Grandview Road
Skillman, NJ 08558-9418
908-874-1666 (Consumer Graphics Dept. Fax)

- This proof indicates approximate color only!
- All colors print 100% unless otherwise indicated.
- All structure and holding lines do not print unless otherwise indicated.
- This is prepared as a color digital mechanical, no traps have been made.
- All trapping is the responsibility of the engraver and/or separator and/or printer.

ARTWORK SPECIFICS

Colors: 6 Note: All colors for reference only, printer to use pre-approved color drawdowns when printing.

Monistat Dark Blue | PANTONE® 226 | PANTONE® 109
PANTONE® Cool Grey 10 | PANTONE® Purple | MATCH GOLD

Fonts: Helvetica,Trade Gothic
Minion Bold, Helvetica Bold
Helvetica Condensed Bold
Zapf Humanist 601 BT Demi
Helvetica 53 Extended
Frutiger 65 Bold, OCR-B
Arial Black, ITC Zapf Dingbats
Didot

Consumer
Graphics Manager: Bryan Petersen
Phone: 908-874-2992

FDA STANDARD SIZES for Drug Facts

12 point Helvetica Bold Italic Title
10 point Helvetica Bold Italic Title (2nd column)
8 point Helvetica Bold Italic Headings
8 point Helvetica Condensed Med "Continued"
6 point Helvetica Bold Subheads
6 point Helvetica Regular Text
6.5 point Leading

2.5 point box hairline
2.5 point hairline
0.5 point hairline
5 point ITC Zapf Dingbats Bullet n

Manufactured Gold is needed for rules
try to create with
(109 / 100%) – (Cool Grey 18%) – (226 / 8%)

Consumer Information Leaflet

624-10-403-3

MONISTAT® 1
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (1200mg) *and* Miconazole Nitrate Cream (2%)

VAGINAL ANTIFUNGAL

Cures Most Vaginal Yeast Infections

and Relieves Associated External Itching and Irritation

Why should I use MONISTAT® 1 Combination Pack with Prefilled Applicator?

MONISTAT® 1 Combination Pack with Prefilled Applicator contains a 1-dose OVULE® Insert that cures most vaginal yeast infections, plus an external cream that can be used for relief of itching and irritation on the skin outside the vagina (vulva) due to a yeast infection. ***Do not use MONISTAT® 1 Combination Pack with Prefilled Applicator if this is the first time you have vaginal discharge, itching, burning and discomfort. See your doctor or health professional first to find out the cause of your symptoms.*** If a doctor has told you in the past that you had a vaginal yeast infection and you have the same symptoms now (such as vaginal discharge, itching or burning), then MONISTAT® 1 Combination Pack with Prefilled Applicator may work for you.

What is a vaginal yeast infection?

A vaginal yeast infection is a common condition caused by an overgrowth of yeast (Candida) that may normally live in the vagina. Your doctor may call this infection "monilia" or "candidiasis." Some women may have a yeast infection on the skin outside of the vagina (vulva) at the same time that they have a vaginal infection.

Who can get a vaginal yeast infection?

You can get a vaginal yeast infection at any age. It is most common during the childbearing years. Women who are pregnant or diabetic, taking antibiotics, birth control pills or steroids, or who have a weakened immune system are more likely to get repeated yeast infections that may not clear up easily with proper treatment.

Some medical conditions can weaken the body's normal ability to fight infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV – the virus that causes AIDS). The HIV virus causes the body to be more likely to get infections, including vaginal yeast infections that may not clear up easily with proper treatment. If you may have been exposed to HIV and get repeated vaginal yeast infections, you should see your doctor right away. For more information on HIV infection, please contact your doctor or the CDC National AIDS HOTLINE. The CDC phone numbers are: 1-800-342-AIDS (English), 1-800-344-7432 (Spanish), or 1-800-243-7889 (hearing impaired, TDD).

How can I tell if I have a vaginal yeast infection?

When you have a vaginal yeast infection, you may have one or more of the following symptoms:

- vaginal itching
- vaginal discharge that may be thick, white, and lumpy like cottage cheese
- vaginal soreness, irritation, or burning
- rash or redness on the skin outside the vagina (vulva)
- burning on urination
- painful vaginal intercourse (sex)

Note: Vaginal yeast infections do NOT cause fever, chills, lower abdominal, back or shoulder pain, foul-smelling vaginal discharge, or a missed period. These may be signs of a sexually transmitted disease (STD) or a tubal pregnancy. If you have these symptoms, call your doctor right away.

What are other causes of a vaginal discharge?

It is normal to have a small amount of vaginal discharge at certain times of the month. This normal discharge may be clear or slightly white and does not cause itching, pain or a foul odor.

The most common cause of an abnormal vaginal discharge is an infection. These infections include bacterial vaginosis (BV), trichomoniasis (Trich), gonorrhea (GC) and/or chlamydia. All of these may be transmitted sexually and are called sexually transmitted diseases (STDs). If you have more questions about sexually transmitted diseases (STDs) call the CDC STD Hotline at 1-800-227-8922.

Although many of the infections mentioned above can cause symptoms similar to a vaginal yeast infection (vaginal discharge, irritation and itching), their diagnosis must be made by a doctor so that proper treatment can be given.

If these infections are not properly treated or if proper treatment is delayed, serious problems, such as pelvic inflammatory disease (PID) may result, which may prevent you from having children in the future. If you are pregnant and do not get the proper treatment, the infection may be passed to your baby before or during delivery and may cause your baby to have permanent damage. If you have multiple sex partners or a new sex partner, you should also ask a doctor before use to make sure you do not have an STD.

Why do women get repeated vaginal yeast infections?

Women may get repeated vaginal yeast infections that may not clear up easily with proper treatment. Listed below are some of the causes of repeated yeast infections:

- **hormonal changes** occurring a few days before the monthly period
- **use of antibiotics**
- **use of some birth control pills**
- **pregnancy**
- **diabetes ("sugar" or "high blood sugar")**
- **clothing** – wearing tight layers or moist clothing in the genital area
- **weakened immune system** – some drugs (such as chemotherapy or steroids) and medical conditions can weaken the body's normal ability to fight infection. One of the most serious of these conditions is infection with the human immunodeficiency virus (HIV – the virus that causes AIDS). Infection with HIV causes the person to be more likely to get infections, including vaginal yeast infections.

If you get vaginal yeast infections often (such as once a month or 3 in 6 months), you should talk to a doctor.

Are vaginal yeast infections sexually transmitted?

Vaginal yeast infections are usually not spread by having intercourse (sex). However, if your partner has a rash, itching or discomfort in his genital area, he should contact a doctor to find out the cause of his symptoms and tell the doctor that you are treating your vaginal yeast infection with MONISTAT® 1 Combination Pack with Prefilled Applicator.

How can I prevent repeated vaginal yeast infections?

To lower your chances of getting another yeast infection:

- **Try to keep the genital area cool and dry.** Yeast grow well in warm, moist areas. The following suggestions may be helpful:

(1) Wear cotton underwear and loose-fitting clothes.

(2) Change out of damp clothes or a wet bathing suit as soon as possible.

(3) If you use minipads when you are not having a menstrual period, change the minipads often.

- **Talk with your doctor about any drugs you are now taking.** You are more likely to get a vaginal yeast infection if you are taking certain drugs such as antibiotics, steroids, or birth control pills. Do not stop taking these drugs without first asking your doctor. A doctor may need to see you to make sure that you do not have other medical conditions such as diabetes or a weakened immune system.

Can I use MONISTAT® 1 Combination Pack with Prefilled Applicator during my menstrual period?

Yes, this product can be used during your menstrual period. In fact, many women get vaginal yeast infections just before their period because of hormonal changes. Using MONISTAT® 1 Combination Pack with Prefilled Applicator during your period will not affect how well this product works. If you have started treatment and your period occurs, you should complete the full course of treatment.

Do not use tampons while using this product, because tampons may remove some of the drug from the vagina. Use deodorant-free sanitary napkins or pads instead, and change them often.

Can I use other vaginal products with MONISTAT® 1 Combination Pack with Prefilled Applicator?

This drug should **not** be used with other vaginal products.

- Douches and tampons may remove some of the OVULE® Insert from the vagina.
- Spermicides may interfere with MONISTAT® 1 Combination Pack with Prefilled Applicator.
- Condoms and diaphragms may be damaged by this product and fail to prevent pregnancy or sexually transmitted diseases (STDs).

Brand	- Monistat	**File name**	- Mon1ComboInsert	**Design Agency Reference**	- SEVEN
Category	- Vaginal Antifungal	**Dieline No.**	- n/a	**Project Name**	- Daytime
Product Variant	- Prefilled (Ovual Insert) Combination	**Barcode No.** (+ BWR & Mag)	- n/a	**Artwork program**	- Illustrator 8.0
Component Type	- Insert	**Seven Job No.**	- 6069/2314	**Lead Mktg. Country**	- USA
Consumer Unit Contents	-	**Formulation No.**	- n/a	**Sales Region**	- North America
Copy & Graphics Number	- XXXXXX	**Printer**	- PCI Triline	**Manufacturing Site**	- PSGA
Version#	- 2	**No. of Colours**	- 2	**Library**	- Local Market Artwork
Date	- 8/17/04	**Print Method**	- offset	**Keywords (Market)**	- XXXXXX

Johnson & Johnson
199 Grandview Road
Skillman, NJ 08558-9418
908-874-1666 (Consumer Graphics Dept. Fax)

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ARTWORK SPECIFICS

Colors: 2
Note: All colors for reference only, printer to use pre-approved color drawdowns when printing.

PANTONE® 300 | PANTONE® Cl Gy 10

Fonts:
Optima / MathPi / Helv. Condensed
Helv. Neue / Helv. Neue Condensed
Helv. Neue Extended, Helv. Condensed-Italic, Helv. Roman

Consumer
Graphics Manager: Bridgette Motley
Phone: 908.874.2736

How can I get the best results when treating my infection?

- Use the Applicator containing the OVULE® Insert, even during your menstrual period.
- Use the tube of cream externally only while symptoms are present. If you have symptoms (such as itching and irritation) on the skin outside the vagina (vulva), apply the cream externally 2 times a day, up to a total of 7 days, as needed.
- Dry the genital area thoroughly after a shower, bath or swim. Change out of a wet bathing suit or damp clothes as soon as possible. A dry area is less likely to lead to the overgrowth of yeast.
- Wear cotton underwear and loose-fitting clothes.
- Wipe from front to back after a bowel movement or after urination.
- Do not douche, because douching may wash the drug out of the vagina.
- Do not use tampons, because they remove some of the drug from the vagina. Use deodorant-free sanitary napkins or pads as needed.
- Do not use spermicides, as they may interfere with MONISTAT® 1 Combination Pack with Prefilled Applicator.
- Do not have vaginal intercourse while using MONISTAT® 1 Combination Pack with Prefilled Applicator.
- Do not scratch the skin outside the vagina. Scratching can cause more irritation and can spread the infection.
- **Tell your doctor about any drugs you are now taking**. Certain drugs such as antibiotics, steroids, and birth control pills, may make it more likely for you to get a vaginal yeast infection. If you are taking any of these drugs do not stop taking them without first asking a doctor.
- If you have any other medical questions or concerns about vaginal yeast infections, call your doctor.

What warnings should I know about when using MONISTAT® 1 Combination Pack with Prefilled Applicator?

For vaginal use only.

Do not use if you have never had a vaginal yeast infection diagnosed by a doctor.

Ask a doctor before use if you have:

- **vaginal itching and discomfort for the first time. You may need a different treatment.**
- **lower abdominal, back or shoulder pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge. You could have a more serious condition.**
- vaginal yeast infections often (such as once a month or 3 in 6 months). You could be pregnant or have a serious underlying medical cause for your symptoms, including diabetes or a weakened immune system.
- been exposed to the human immunodeficiency virus (HIV) that causes AIDS.

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine, warfarin (coumadin), because bleeding or bruising may occur.

6-DIGIT BAR CODE 1/2" HEIGHT

When using this product:

- do not use tampons, douches, spermicides, or other vaginal products. Condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases (STDs).
- do not have vaginal intercourse
- mild increase in vaginal burning, itching or irritation may occur

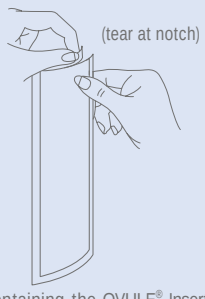
How Should I Use MONISTAT® 1 Combination Pack with Prefilled Applicator?

This product is for adults and children 12 years of age and over. For children under 12 years, ask a doctor.

Directions for using the Applicator containing the OVULE® Insert :

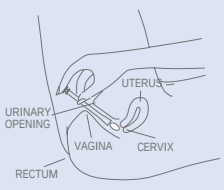
1 Open pouch and remove Prefilled Applicator. (see picture).

KEEP CONTENTS DRY BEFORE USE.



2 Hold the Applicator containing the OVULE® Insert by the opposite end from where the OVULE® Insert is located.

3 Gently insert the applicator into the vagina as far as it will go comfortably. This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent, as shown in the picture.



4 With one hand holding the barrel, use the other hand to push the plunger all the way in to place the OVULE® Insert as far back in the vagina as possible. Then remove both parts of the applicator from the vagina.

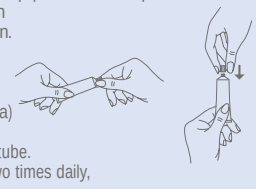
5 Throw away applicator after use. Do not flush in toilet.

You may want to use deodorant-free pads or pantyshields to protect your clothing during the time that you are using MONISTAT® 1 Combination Pack with Prefilled Applicator. This is because the OVULE® Insert can leak or you may get some discharge. **Do not use tampons, douches, spermicides, condoms or diaphragms** until after you have completed the treatment and your symptoms are gone.

Directions for using the External Vulvar Cream

Use the cream twice daily, for up to 7 days as needed.

1. Open the tube by unscrewing the cap. The first time the tube is opened, press the sharp point of the cap into the sealed end of the tube. Push down firmly until the seal is open.
2. Squeeze a small amount of cream onto your fingertip.
3. Apply the cream onto the skin outside the vagina (vulva) that itches and is irritated.
4. Screw the cap back on the tube.
5. Repeat steps 2 – 4, up to two times daily, as needed.



Stop use and ask your doctor if:

- **symptoms do not get better in 3 days**
- **symptoms last more than 7 days**
- **you get a rash or hives, abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge.**

These may be signs that this product is not working, or you may have a more serious condition or an allergic reaction.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

What side effects may occur with MONISTAT® 1 Combination Pack with Prefilled Applicator?

A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE® Insert is inserted. Abdominal cramping has also been reported.

Stop using MONISTAT®1 Combination Pack with Prefilled Applicator and consult your doctor if you have abdominal pain, hives, skin rash, or if you have severe vaginal burning, itching, or irritation or swelling.

What should I do if I have questions about MONISTAT® 1 Combination Pack with Prefilled Applicator?

Questions of a medical nature should be taken up with your doctor. If you have any other questions or need more information on this product, call our toll-free number. Call between 8:00 AM and 5:00 PM Eastern time, Monday through Friday. A health care specialist will gladly answer your questions. Our toll-free number is 1-877-MONISTAT (1-877-666-4782).

Other Information:

- **TAMPER-EVIDENT UNIT – do not use if printed sealed pouch is torn, open or incompletely sealed**.
- do not use if tube seal has been punctured or embossed design ▽ symbol is not visible.
- store at 20° – 25° C (68° – 77° F)
- this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days.

Active ingredients: OVULE® Insert: miconazole nitrate, 1200 mg. External Vulvar Cream – miconazole nitrate, 2%.

Inactive ingredients: OVULE® Insert: gelatin, glycerin, lecithin, mineral oil, titanium dioxide, white petrolatum. External Vulvar Cream: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol.

Distributed by:
Personal Products Company
Division of McNeil-PPC, Inc.
Skillman, NJ 08558

624-10-403-3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

LABELING REVIEWS

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-308/S-009 (SE2)**
Submission Date:	December 2, 2003 (CDER stamp date December 3, 2003)
Type of Submission:	Labeling supplement with clinical data
Sponsor:	Personal Products Company (PPC), Division of McNeil-PPC, Inc.
Drug Product:	Monistat® 1 (miconazole nitrate) Combination Pack
Active Ingredient:	•Miconazole nitrate 1200 mg (in each vaginal insert) •Miconazole nitrate 2% (external cream)
Indications:	•treats vaginal yeast infections (1-dose treatment) •relieves external itching and irritation due to a vaginal yeast infection
Stock Keeping Units:	2 (1 prefilled disposable applicator plus one 9 gram tube external cream; one disposable applicator and ovule insert plus one 9 gram tube external cream)
Review Date:	July 20, 2004
Reviewer:	Arlene Solbeck HFD-560
Project Manager:	Leah Cutter

Background

NDA 21-208 Timeline:

- Approved for OTC use on June 29, 2001 for the treatment of vulvovaginal candidiasis as Monistat® 1 Combination Pack.. Consisted of a miconazole nitrate (1200 mg) soft gel vaginal insert and 2% miconazole nitrate cream for external use. Required consumers to manually load the applicator with the vaginal insert before use.
- SCP-004 approved on September 6, 2002 as one vaginal insert (Ovule™) (miconazole nitrate, 1200 mg) prefilled applicator for vaginal internal use and a 9 gram tube of miconazole nitrate (2%) cream for external use . Prefilled applicator and 9 gram tube of cream placed into a packing tray (the primary package) and secured with a printed seal.
- SCP-005 approved on 11/20/02 to change the secondary packaging to provide an additional measure of moisture protection to the vaginal insert (Ovule™). Provided for the packing tray to be sealed inside an aluminum pouch (the secondary package) along with a 3 gram packet of silica desiccant. Desiccant to be outside of the primary package (the packing tray) and not in contact with the product.
- SCP-008 approved on 12/3/03 to change the packaging so that the current secondary packaging (over pouch) becomes the primary container/closure system (e.g. prefilled applicator sealed inside an aluminum pouch rather than inside a packing tray with a printed seal and no silica desiccant in the pouch).

This current submission, S-009, was submitted for approval to change the label instructions to allow for daytime administration of the drug product in addition to the current bedtime administration. The sponsor submitted draft labeling (carton and package insert) for both SKUs (non-prefilled Monistat®1 Combination Pack (original submission) and prefilled applicator Monistat®1 Combination Pack (S-004/005)).

I. Reviewer's Comments

A. Carton and Drug Facts Labeling

These comments apply to both SKUs, unless otherwise noted.

1. Non-prefilled SKU: a flag on the fifth panel which stated "**The Only** 1-Day with External Cream for **Itch Relief**" was removed and the following statement was added "ONE TREATMENT OVULE™ Insert plus External Cream for Itch Relief". This is acceptable.

2. Prefilled SKU: a flag on the fifth panel which stated "Convenient Prefilled Applicator" was removed and the following statement was added "ONE

TREATMENT OVULE™ Insert Prefilled Applicator Plus External Cream for Itch Relief". This is acceptable.

3. Both SKUs: on the fifth panel, the following phrases were added:
   DAY *or* NIGHT
   STAYS IN PLACE
   This is acceptable.

4. Both SKUS: on the principal display panel (PDP) a circle symbol stating "CLINICALLY PROVEN" containing the Ortho Symbol was added. This is acceptable.

5. Both SKUs: on the PDP, the Ortho symbol and a statement of quantity of contents (Net. Wt. 1 OVULE™ Insert + 0.32 oz. (9g) Tube) was added. This is acceptable.

6. Non-prefilled SKU: the tamper-evident feature statement located in a box on the bottom panel the carton reads "DO NOT USE IF **PRINTED** SEALED POUCH OR SEALED VAGINAL INSERT BLISTER IS TORN, OPEN OR INCOMPLETELY SEALED. This is acceptable.

7. Both SKUs: in *Drug Facts* in ***Directions***, the statement for use of the vaginal insert was revised from "with the applicator place the vaginal insert into the vagina at bedtime" to read "with the applicator place the vaginal insert into the vagina." This is acceptable.

8. Non-prefilled SKU: in *Drug Facts* in ***Other information***, the first bulleted statement was revised to read "do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed. This is acceptable except that the sponsor should bold the word "printed" to be consistent with the carton labeling.

9. Non-prefilled SKU: we note that the spacing for the headings *Drug Facts* and *Drug Facts* (continued) as well as the subheadings ***Directions, Other information, Inactive ingredients*** and ***Questions*** need to be revised. Remove the extra space between the "F" and "a" in *Drug Facts*. Remove the extra space between "***Drug Facts***" and "(continued)". Left justify ***Directions***. Remove the extra space between "Other" and "information" in ***Other information***. Remove the extra space between the "I" and "nactive" in ***Inactive ingredients*** and between both words of the subheading. Remove the extra spaces between the "Q" and "uestions?" in ***Questions?***. Delete the space between the third and fourth bulleted statements in **Ask a doctor before use if you have**.

10. Both SKUS: realign "***Purpose***" with the "I" in "Vaginal antifungal".

11. Both SKUs: Add the following "expectation of benefit for 1-day products" bulleted statement under ***Other information*** to read as follow:: "this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

B. Consumer Information Leaflet

12. Prefilled Applicator SKU: in the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable.

13. Non-prefilled SKU: in the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE® Insert, even during your menstrual period." Since this is not the prefilled applicator SKU, the statement should read "Use the OVULE® Insert, even during your menstrual period."

14. Non-prefilled SKU: under **What side effects may occur with Monistat®1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE® Insert is inserted. Since this is not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching or irritation may occur when the OVULE® Insert is inserted."

15. Non-prefilled SKU: under **Other information**, the tamper-evident statement was revised to read "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or vaginal blister is torn, open or incompletely sealed.**" This should be revised to be consistent with carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed)**".

16. Prefilled SKU: in the section **Directions for using the Applicator containing the OVULE™ Insert**, the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture. This is acceptable except that we would recommend "As shown in the picture" to be part of the sentence "Or, you can lie on your back with your knees bent."

17. Non-prefilled SKU: See #15. This also applies to the non-prefilled SKU, direction #5, under **Directions for using the Applicator and the OVULE® Insert**. Also under this section, a new direction (#1) was added to direct consumers in how to open the tamper-evident pouch containing the insert and the

applicator. As a result, the rest of the directions were renumbered. This is acceptable.

18. Both SKUs: the statement in the **Directions** to lie down as soon as possible after inserting the insert to reduce leakage was deleted. This is acceptable since this drug treatment is for day or night use.

19. Both SKUs: in the section **Directions for using the External Vulvar Cream,** the fifth direction was revised from "Repeat steps 2-4, each morning and at bedtime for up to 7 days" to "Repeat steps 2-4, up to two times daily, as needed." This is acceptable.

20. Both SKUs: add the following "expectation of benefit for 1-day products" bulleted statement under ***Other information*** to read as follow:: "this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days." This is to be consistent with carton labeling.

C. Pouch

The pouch labeling was not part of the submission. The sponsor sent the pouch labeling separately. It is acceptable.

II. Reviewer's Recommendations

The following comments can be conveyed to the sponsor:

A. Pouch: The pouch labeling is acceptable.

B. Carton and Drug Facts:

1. Non-prefilled SKU: bold the word "printed" in first bulleted statement in ***Other information*** to be consistent with the carton labeling.
2. Non-prefilled SKU:
   - Remove the extra space between the "F" and "a" in "*Drug Facts*".
   - Remove the extra space between "*Drug Facts*" and "(continued)".
   - Left justify "***Directions***".
   - Remove the extra space between "Other" and "information" in "***Other information***".
   - Remove the extra space between the "I" and "nactive" in "***Inactive ingredients***" and between both words of the subheading.
   - Remove the extra spaces between the "Q" and "uestions?" in "***Questions?***"
   - Delete the space between the third and fourth bulleted statements under "**Ask a doctor before use if you have**".
3. Both SKUS: realign "***Purpose***" with the "I" in "Vaginal antifungal".

4. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

D. Consumer Information Leaflet:

5. Non-prefilled SKU: In the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE ® Insert, even during your menstrual period." Since this is not the prefilled applicator SKU, the statement should read "Use the OVULE® Insert, even during your menstrual period." Revise this statement.

6. Non-prefilled SKU: Under **What side effects may occur with Monistat®1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE® Insert is inserted. Since this is not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching or irritation may occur when the OVULE® Insert is inserted."

7. Both SKUs: for the prefilled SKU under **Directions for using the Applicator containing the OVULE™ Insert,** the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture. This is acceptable except that we would recommend "As shown in the picture" to be part of the sentence "Or, you can lie on your back with your knees bent." Revise the same direction for the non-prefilled SKU. It is direction #5.

8. Non-prefilled SKU: under ***Other information***, revise the Tamper-Evident Unit statement to be consistent with the carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed)**".

9. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

APPEARS THIS WAY
ON ORIGINAL

Arlene Solbeck 7/28/04

Arlene Solbeck, MS
IDS/Biologist, HFD-560

Helen Cothran 7/28/04

Helen Cothran, BS
Team Leader, HFD-560

Attachments

APPEARS THIS WAY
ON ORIGINAL

NDA 21-308/SCP009
HFD-590: Weikel/Roca/Meyer/Albrecht
HFD-560: Division File
HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/ Hu/Cutter/Hillfiker
DOCID: 21803scp009.doc

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/s/

Arlene Solbeck
7/28/04 03:32:36 PM
INTERDISCIPLINARY

Helen Cothran
7/29/04 09:10:28 AM
INTERDISCIPLINARY

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-308/S-009 (SE2)**
Submission Date:	August 18, 2004 (CDER stamp date August 19, 2004)
Type of Submission:	Amendment to Labeling supplement with clinical data
Sponsor:	Personal Products Company (PPC), Division of McNeil-PPC, Inc.
Drug Product:	Monistat® 1 (miconazole nitrate) Combination Pack
Active Ingredient:	•Miconazole nitrate 1200 mg (in each vaginal insert) •Miconazole nitrate 2% (external cream)
Indications:	•treats vaginal yeast infections (1-dose treatment) •relieves external itching and irritation due to a vaginal yeast infection
Stock Keeping Units:	2 (1 prefilled disposable applicator plus one 9 gram tube external cream; one disposable applicator and ovule insert plus one 9 gram tube external cream)
Review Date:	August 24, 2004
Reviewer:	Arlene Solbeck HFD-560
Project Manager:	Leah Cutter

Background

NDA 21-208 Timeline:

- Approved for OTC use on June 29, 2001 for the treatment of vulvovaginal candidiasis as Monistat® 1 Combination Pack. Consisted of a miconazole nitrate (1200 mg) soft gel vaginal insert and 2% miconazole nitrate cream for external use. Required consumers to manually load the applicator with the vaginal insert before use.
- SCP-004 approved on September 6, 2002 as one vaginal insert (Ovule™) (miconazole nitrate, 1200 mg) prefilled applicator for vaginal internal use and a 9 gram tube of miconazole nitrate (2%) cream for external use . Prefilled applicator and 9 gram tube of cream placed into a packing tray (the primary package) and secured with a printed seal.
- SCP-005 approved on 11/20/02 to change the secondary packaging to provide an additional measure of moisture protection to the vaginal insert (Ovule™). Provided for the packing tray to be sealed inside an aluminum pouch (the secondary package) along with a 3 gram packet of silica desiccant. Desiccant to be outside of the primary package (the packing tray) and not in contact with the product.
- SCP-008 approved on 12/3/03 to change the packaging so that the current secondary packaging (over pouch) becomes the primary container/closure system (e.g. prefilled applicator sealed inside an aluminum pouch rather than inside a packing tray with a printed seal and no silica desiccant in the pouch).

S-009 was submitted for approval on December 2, 2003 to change the label instructions to allow for daytime administration of the drug product in addition to the current bedtime administration. The sponsor submitted draft labeling (carton and package insert) for both SKUs (non-prefilled Monistat®1 Combination Pack (original submission) and prefilled applicator Monistat®1 Combination Pack (S-004/005)). A label review was placed into DFS on July 29, 2004. Labeling comments were faxed to the sponsor on August 3, 2004. This current submission is the sponsor's updated draft labeling in response to FDA's August 3rd fax.

I. Reviewer's Comments

The following comments were conveyed to the sponsor:

A. Carton and Drug Facts:

1. Non-prefilled SKU: bold the word "printed" in first bulleted statement in ***Other information*** to be consistent with the carton labeling.

Sponsor'response: Sponsor bolded the word "printed in the first bulleted statement in Other information. This is acceptable.

2. Non-prefilled SKU:

- Remove the extra space between the "F" and "a" in "*Drug Facts*".

Sponsor's response: Sponsor removed the extra spaces. This is acceptable.

- Remove the extra space between "*Drug Facts*" and "(continued)".

Sponsor's response: Sponsor removed the extra space. This is acceptable.

- Left justify "***Directions***".

Sponsor's response: Sponsor left justified "***Directions***". This is acceptable.

- Remove the extra space between "Other" and "information" in "***Other information***".

Sponsor's response: Sponsor removed the extra space. This is acceptable.

- Remove the extra space between the "I" and "nactive" in "***Inactive ingredients***" and between both words of the subheading.

Sponsor's response: Sponsor removed the extra spaces. This is acceptable.

- Remove the extra spaces between the "Q" and "uestions?" in "***Questions?***"

Sponsor's response: Sponsor removed the extra spaces. This is acceptable.

- Delete the space between the third and fourth bulleted statements under "**Ask a doctor before use if you have**".

Sponsor's response: Sponsor removed the extra space. This is acceptable.

3. Both SKUS: realign "***Purpose***" with the "I" in "Vaginal antifungal".
Sponsor's response: Sponsor realigned "Purpose" with the "I" in "Vaginal antifungal" for both SKUs as requested. This is acceptable.

4. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

Sponsor's response: Sponsor added the "expectation of benefit statement for 1-day products" to both SKUs as requested. This is acceptable.

B. Consumer Information Leaflet:

5. Non-prefilled SKU: In the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE ® Insert, even during your menstrual period." Since this is not the prefilled applicator SKU, the statement should read "Use the OVULE® Insert, even during your menstrual period." Revise this statement.

Sponsor's response: Sponsor revised the first bulleted statement in the section **How can I get the best results when treating my infection?** as requested. This is acceptable.

6. Non-prefilled SKU: Under **What side effects may occur with Monistat®1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE® Insert is inserted. Since this is not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching or irritation may occur when the OVULE® Insert is inserted." Revise this statement.

Sponsor's response: The sponsor revised the first sentence under **What side effects may occur with Monistat®1 Combination Pack?** as requested. This is acceptable.

7. Both SKUs: For the prefilled SKU under **Directions for using the Applicator containing the OVULE™ Insert**, the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture." This is acceptable except that we would recommend "As shown in the picture" to be part of the sentence "Or, you can lie on your back with your knees bent." Revise the same direction for the non-prefilled SKU. It is direction #5.

Sponsor's response: The sponsor revised direction #3 for the prefilled SKU and direction #5 for the nonprefilled SKU as requested. This is acceptable.

8. Non-prefilled SKU: Under **Other information**, revise the Tamper-Evident Unit statement to be consistent with the carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed**").

Sponsor's response: Sponsor revised the Tamper-Evident Unit statement as requested. This is acceptable.

9. Both SKUs: Add the following "expectation of benefit for 1-day products" under **Other information** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

Sponsor's response: Sponsor added the "expectation of benefit statement for 1-day products" to both SKUs as requested. This is acceptable.

II. Reviewer's Comments

The labeling for both the prefilled applicator SKU and nonprefilled applicator SKU for Monistat®1 Combination Pack under NDA 21-308 S-009 is acceptable. No further changes need to be made for approval.

APPEARS THIS WAY
ON ORIGINAL

8/24/04

Arlene Solbeck, MS
IDS/Biologist, HFD-560

8/25/04

Helen Cothran, BS
Team Leader, HFD-560

Attachments

APPEARS THIS WAY
ON ORIGINAL

NDA 21-308/SCP009
HFD-590: Weikel/Roca/Meyer/Albrecht
HFD-560: Division File
HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/ Hu/Cutter/Hillfiker
DOCID: 21803scp009A.doc

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/s/

Arlene Solbeck
8/27/04 09:21:52 AM
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Helen Cothran
8/27/04 09:44:37 AM
INTERDISCIPLINARY

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration

NDA#:	**21-308/S-009 (SE2) BL**
Submission Date:	September 7, 2004 (CDER stamp date September 8, 2004)
Type of Submission:	Amendment to Prior Approval Supplement
Sponsor:	Personal Products Company (PPC), Division of McNeil-PPC, Inc.
Drug Product:	Monistat® 1 (miconazole nitrate) Combination Pack
Active Ingredient:	•Miconazole nitrate 1200 mg (in each vaginal insert) •Miconazole nitrate 2% (external cream)
Indications:	•treats vaginal yeast infections (1-dose treatment) •relieves external itching and irritation due to a vaginal yeast infection
Stock Keeping Units:	2 (1 prefilled disposable applicator plus one 9 gram tube external cream; one disposable applicator and ovule insert plus one 9 gram tube external cream)
Review Date:	September 20, 2004
Reviewer:	Arlene Solbeck HFD-560
Project Manager:	Leah Cutter

Background

NDA 21-208 Timeline:

- Approved for OTC use on June 29, 2001 for the treatment of vulvovaginal candidiasis as Monistat® 1 Combination Pack. Consisted of a miconazole nitrate (1200 mg) soft gel vaginal insert and 2% miconazole nitrate cream for external use. Required consumers to manually load the applicator with the vaginal insert before use.
- SCP-004 approved on September 6, 2002 as one vaginal insert (Ovule™) (miconazole nitrate, 1200 mg) prefilled applicator for vaginal internal use and a 9 gram tube of miconazole nitrate (2%) cream for external use . Prefilled applicator and 9 gram tube of cream placed into a packing tray (the primary package) and secured with a printed seal.
- SCP-005 approved on 11/20/02 to change the secondary packaging to provide an additional measure of moisture protection to the vaginal insert (Ovule™). Provided for the packing tray to be sealed inside an aluminum pouch (the secondary package) along with a 3 gram packet of silica desiccant. Desiccant to be outside of the primary package (the packing tray) and not in contact with the product.
- SCP-008 approved on 12/3/03 to change the packaging so that the current secondary packaging (over pouch) becomes the primary container/closure system (e.g. prefilled applicator sealed inside an aluminum pouch rather than inside a packing tray with a printed seal and no silica desiccant in the pouch).

S-009 was submitted for approval on December 2, 2003 to change the label instructions to allow for daytime administration of the drug product in addition to the current bedtime administration. The sponsor submitted draft labeling (carton and package insert) for both SKUs (non-prefilled Monistat®1 Combination Pack (original submission) and prefilled applicator Monistat®1 Combination Pack (S-004/005)). A label review was placed into DFS on July 29, 2004. Labeling comments were faxed to the sponsor on August 3, 2004. The sponsor responded with revised labeling on August 18, 2004. A label review was placed into DFS on August 27, 2003 and an e-mail was sent to the sponsor on September 1, 2004 advising them to revise the directions on the carton labeling to allow for daytime administration of the drug product in addition to the current bedtime administration. This submission contains the revised carton labeling.

I. Reviewer's Comments

For both the prefilled and non-prefilled SKUs, the sponsor revised the first statement of the directions for the vaginal insert from "with the applicator place the vaginal insert into the vagina at bedtime." to "with the applicator place the vaginal insert into the vagina." This is acceptable.

II. Reviewer's Recommendations

For both the prefilled and non-prefilled SKUs, the sponsor revised the first statement of the directions for the vaginal insert from "with the applicator place the vaginal insert into the vagina at bedtime." to "with the applicator place the vaginal insert into the vagina." This is acceptable.

The carton labeling for both the prefilled applicator SKU and nonprefilled applicator SKU for Monistat®1 Combination Pack under NDA 21-308 S-009 is acceptable. No further changes need to be made for approval.

Arlene Solbeck 9/22/04

Arlene Solbeck, MS
IDS/Biologist, HFD-560

Helen Cothran

Helen Cothran, BS
Team Leader, HFD-560

Attachments

NDA 21-308/SE2-009BL
HFD-590: Weikel/Roca/Meyer/Albrecht
HFD-560: Division File
HFD-560: Ganley/Rosebraugh/Solbeck/Cothran/Segal/ Hu/Cutter/Hillfiker
DOCID: 21308scp009A2.doc

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/s/

Arlene Solbeck
9/22/04 08:47:27 AM
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Helen Cothran
9/22/04 02:16:15 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

CLINICAL / MEDICAL REVIEW

CLINICAL REVIEW

Application Type	21-308
Submission Number	S-009
Submission Code	SE 8
Letter Date	December 2, 2003
Stamp Date	December 3, 2003
PDUFA Goal Date	October 3, 2004
Reviewer Name	Joette M. Meyer, Pharm.D.
Review Completion Date	September 17, 2004
Established Name	Miconazole Nitrate Vaginal Insert and Cream
(Proposed) Trade Name	Monistat® 1 Combination Pack
Therapeutic Class	Vaginal Anti-fungal
Applicant	Personal Products Company
Priority Designation	S
Formulation	Miconazole Nitrate Vaginal Insert 1200 mg and Miconazole Nitrate Cream 2%
Dosing Regimen	One vaginal insert plus external cream twice daily for up to 7 days, as needed
Indication	Vulvovaginal Candidiasis (VVC)
Intended Population	Adult, Otherwise Healthy Women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The combination of miconazole nitrate 1200 mg vaginal Insert (ovule) and 2% external vulvar cream was approved first as a prescription drug product for the treatment of vulvovaginal candidiasis (VVC) in June 1999 (Monistat® Dual-Pak™; NDA 20-968) and then subsequently approved for use over-the-counter (OTC) in June 2001 (Monistat® 1 Combination Pack; NDA 21-308). Both products were specifically labeled for use "at bedtime".

The applicant believes that daytime administration provides a more convenient treatment option compared to bedtime administration because patients can begin treatment immediately, rather than waiting until bedtime to administer the product. Therefore, in the current submission, the applicant is requesting the words "at bedtime" be removed from the current labeling.

A clinical study (Protocol CA-P-2343) of 573 otherwise healthy female subjects with VVC was conducted by the applicant to demonstrate the safety and efficacy of daytime administration of the product. Subjects were randomized to self-administer the ovule either at bedtime or during the daytime and were allowed to apply the external cream twice a day for up to 7 days. The primary efficacy endpoint was therapeutic cure (a combination of clinical and mycological cure) at the Test-of-Cure visit which was conducted 21 to 30 days after intravaginal study drug administration. A non-inferiority comparison between the daytime and bedtime groups was performed and the two treatment groups were to be considered non-inferior if the lower bound of the 95% confidence interval of the treatment difference (Daytime minus Bedtime) was above -15%.

The therapeutic cure rates for subjects evaluable for efficacy at the Test-of-Cure Visit were 57.5% (86/149) in the Daytime group and 50.9% (83/163) in the Bedtime group, with a 95% confidence interval of (-4.6%, 18.2%). The lower bound of the 95% confidence interval was greater than -15%; therefore, the daytime administration is considered non-inferior to bedtime administration. In addition, therapeutic cure rates were not significantly different between subjects with a low activity level (60.5% [26/43]) compared to a high activity level (56.2% [59/105]) ($p = 0.7154$).

Treatment-emergent adverse events observed in this study were consistent with the known safety profile of miconazole nitrate. There was no appreciable difference in the incidence of adverse events between treatment schedules. Two subjects (one in each group) had treatment-related adverse events that led to subject discontinuation. There were three serious adverse events reported during the study, all of which were considered not related or of unlikely relationship to study drug. No subject died during the study.

In summary, miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (together as Monistat 1 Combination Pack) are safe and effective for daytime use for the treatment of vulvovaginal candidiasis in otherwise healthy adult women.

1.2 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	Miconazole Nitrate Vaginal Insert and Cream
Trade Name	Monistat® 1 Combination Pack
Therapeutic Class	Vaginal Anti-fungal
Applicant	Personal Products Company
Priority Designation	S
Formulation	Miconazole Nitrate Vaginal Insert 1200 mg and Miconazole Nitrate Cream 2%
Dosing Regimen	One vaginal insert plus external cream twice daily for up to 7 days, as needed
Indication	Vulvovaginal Candidiasis (VVC)
Intended Population	Adult, Otherwise Healthy Women

1.3.2 Efficacy

Study CA-P-2343 was a multicenter, randomized, investigator-blinded, Phase 3 study of single-dose miconazole nitrate 1200 mg vaginal insert (ovule) in the treatment of VVC in adult,

otherwise healthy women. Subjects were randomly assigned to self-administer the ovule either at bedtime (subsequently remaining in bed for at least 30 minutes) or at a subject-determined convenient time during the day (within six hours after arising). Both treatment groups also received a nine-gram tube of 2% miconazole nitrate external vulvar cream to be applied up to twice daily to the vulvar area, as needed for external symptoms, for a maximum of seven days.

A total 573 subjects were enrolled; 279 were randomized to the Daytime group and 294 were randomized to the Bedtime group. Three subjects were considered nonevaluable for the safety, Intent-to-Treat, or Efficacy Evaluable populations; two subjects (54806 in the Daytime group and 61106 in the Bedtime group) were lost to follow-up, did not return a Daily Diary Card, and had no record of treatment for either the ovule or external cream, and one subject (61906 in the Bedtime group) was randomized, but did not take drug. Therefore, there were 570 subjects in both the safety and Intent-to-Treat populations (278 in the Daytime group and 292 in the Bedtime group).

Slightly less than half of the subjects in the safety and Intent-to-Treat populations were nonevaluable for efficacy and were excluded from the Efficacy Evaluable population in each treatment group (46.6% and 44.6%, respectively).

The primary efficacy endpoint of 'therapeutic cure' was based upon the combination of clinical and mycological cure. The therapeutic cure rates for subjects evaluable for efficacy at the Test-of-Cure Visit (21 to 30 days after intravaginal study drug administration) were 57.5% (86/149) in the Daytime group and 50.9% (83/163) in the Bedtime group, with a 95% confidence interval of the treatment difference (Daytime minus Bedtime) of (-4.6%, 18.2%). The lower bound of the 95% confidence interval was greater than -15%; therefore, the daytime administration is non-inferior to bedtime administration.

Mycological cure rates were 70.5% (105/149) versus 63.8% (104/163), and clinical cure rates were 74.5% (111/149) versus 73.6% (120/163) for the Daytime and Bedtime groups, respectively.

Results for the Intent-to-treat population were lower but consistent with the Efficacy Evaluable population: 43.5% (121/278) in the Daytime group compared to 35.3% (103/292) in the Bedtime group for the therapeutic cure rates [95% CI (0.1%, 16.4%)]; 50.7% (141/278) compared to 44.5% (130/292) for mycological cures; and 70.1% (195/278) compared to 67.1% (196/292) for clinical cures, respectively. Clinical and mycological response rates were positively, but weakly, correlated in both the Intent-to-Treat and Efficacy Evaluable populations.

The therapeutic cure rates at the Test-of-Cure Visit in the Efficacy Evaluable population in the Daytime group were not significantly different between subjects with a low activity level (60.5% [26/43]) compared to a high activity level (56.2% [59/105]) ($p = 0.7154$). Therapeutic cure rates were lower in the Intent-to-Treat population, but also were not significantly different between the low and high activity levels (48.8% [39/80] compared to 43.0% [80/186], $p = 0.4212$).

Comparisons between treatment schedules for the Efficacy Evaluable and Intent-to-Treat populations showed no statistically, or clinically, significant difference between the Daytime and Bedtime groups for the estimated time to relief of itching, burning, and irritation, and for all three symptoms combined.

1.3.3 Safety

Treatment-emergent adverse events observed in this study were consistent with the known safety profile of miconazole nitrate. The reproductive system and breast disorders body system was affected most frequently in both treatment groups, primarily consisting of vulvovaginal discomfort (18.7% [52/278] in the Daytime group and 21.6% [63/292] in the Bedtime group), and most adverse events were mild or moderate in intensity. There was no appreciable difference in the incidence of adverse events between treatment schedules. Two subjects (one in each group) had treatment-related adverse events that led to subject discontinuation. There were three serious adverse events reported during the study, all of which were considered not related or of unlikely relationship to study drug. No subject died during the study.

1.3.4 Dosing Regimen and Administration

According to the applicant, the physiochemical properties of the formulation allow the ovule to remain *in situ* for up to 4 days. These properties include the bioadhesive liquid inside the soft gelatin shell and the adhesive properties of the gelatin shell itself. Therefore, theoretically, daytime administration versus bedtime administration should not affect the retention of the product. In the current submission, the applicant has conducted a clinical study that demonstrated the non-inferiority of daytime versus bedtime administration of the ovule, regardless of a woman's activity level.

1.3.5 Drug-Drug Interactions

Administration of oral or intravenous miconazole with coumarin anticoagulants has previously been shown to produce an enhanced anticoagulant effect. In patients receiving oral anticoagulant therapy, the prothrombin time (PT) or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with miconazole, and should be reassessed periodically during concurrent therapy. Alternatively, an antifungal drug other than an imidazole or triazole, such as nystatin, could be substituted for miconazole.[1]

Since only trace amounts of miconazole are absorbed from the vagina, the potential for a drug interaction between the Monistat 1 Combination Pack and warfarin is unlikely; however, the product is currently labeled such that patients taking coumadin should notify their physician before beginning therapy with the Monistat 1 Combination Pack.

1 DrugDex® - Drug Evaluations. Miconazole. 2004.

1.3.6 Special Populations

1.3.6.1 Efficacy in Special Populations

Differences, if any, seen in the therapeutic cure rates between subjects in the following groups are not considered clinically meaningful: younger (≤ 64 years) and older females (≥ 65 years); and Caucasians, Blacks, and Hispanics. No changes to the recommended dosing of Monistat 1 Combination Pack are warranted based on age or race.

1.3.6.2 Safety in Special Populations

Differences, if any, seen in adverse events reported for subjects in the following groups are not considered clinically meaningful: younger (≤ 64 years) and older females (≥ 65 years); and Caucasians, Blacks, and Hispanics. Reporting of adverse events by age or race is not warranted in the labeling of Monistat 1 Combination Pack.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	Miconazole Nitrate Vaginal Insert and Cream
Trade Name	Monistat® 1 Combination Pack
Therapeutic Class	Vaginal Anti-fungal
Formulation	Miconazole Nitrate Vaginal Insert 1200 mg and Miconazole Nitrate Cream 2%
Dosing Regimen	One vaginal insert plus external cream twice daily for up to 7 days, as needed
Indication	Vulvovaginal Candidiasis (VVC)
Intended Population	Adult, Otherwise Healthy Women
Proposed Labeling	Remove the words "at bedtime" from the product labeling, to allow for daytime or bedtime administration

The applicant explains the physiochemical properties of the ovule as follows:

> The liquid mass of the vaginal ovule consists of 1200 mg of miconazole nitrate in —mL of bioadhesive oil suspension filled into a water-soluble soft gelatin shell. After vaginal insertion, the ovule will adhere to the moist vaginal membrane and react with vaginal fluid. The liquid mass is then released into the vagina in a short period of time (< 15 minutes by USP disintegration method). During this time, the bioadhesive oil suspension will spread and form a sticky layer. Concurrently, the gelatin shell will form a hydrophilic adhesive polymer to enhance the retention of the formulation in the local area. This further enhances the retention of the formulation in the vagina providing an adequate local concentration of miconazole nitrate for treating VVC.

2.2 Currently Available Treatment for Indications

A table of the currently available over-the-counter (OTC) and prescription (Rx) products approved for vaginal candidiasis are shown in the table below.

Anti-Fungal Agent	Trade Name	Dosing Regimen	Comments
Butoconazole	Femstat-3 2% cream	Qhs x 3 days	OTC
	Gynazole-1 butoconazole nitrate vaginal cream, 2%	Single dose	OTC
Clotrimazole	Gyne-Lotrimin 100 mg insert	one insert Qhs x 7 days; or 2 inserts Qhs x 3 days	OTC
	Gyne-Lotrimin 200 mg insert	Qhs x 7 days	
	Gyne-Lotrimin 1% (50 mg) cream	Qhs x 7 days	OTC
	Gyne-Lotrimin Combination Pack (100 mg insert and 1% external cream)	Qhs x 3 days and cream bid prn	OTC
	Gyne-Lotrimin-3 2% (100 mg) cream	Qhs x 3 days	OTC
	Gyne-Lotrimin-1 4% (200 mg) cream	Single dose	OTC
	Mycelex G 100 mg insert	One insert Qhs x 7 days; or 2 inserts Qhs x 3 days	OTC
	Mycelex G 200 mg insert	Qhs x 3 days	Rx Use in pregnancy only
	Mycelex-7 1% cream	Qhs x 7 days	OTC
	Mycelex-1 Twin Pack (500 mg supp and 1% external cream)	Single dose (insert) and cream bid prn	Rx
	Mycelex-7 combination pack (100 mg supp and 1% external cream)	Qhs x 7 days	OTC
	150 mg oral tablet	Single dose	Rx
Fluconazole	Monistat-7 2% (100 mg) cream	Qhs x 7 days	OTC
Miconazole Nitrate	Monistat-7 cream combination pack (2%, 100 mg, intravaginal cream and 2% external vulvar cream)	Qhs x 7 days and cream bid prn	OTC

Anti-Fungal Agent	Trade Name	Dosing Regimen	Comments
	Monistat-7 100 mg supp	Qhs x 7 days	OTC
	Monistat-7 combination pack (100 mg supp and 2% external cream)	Qhs x 7 days and cream bid prn	OTC
	Monistat-3 200 mg supp	Qhs x 3 days	Rx
	Monistat-3 combination pack (200 mg supp and 2% external cream	Qhs x 3 days and cream bid prn	Rx
	Monistat-3 4% (200 mg) cream	Qhs x 3 days	OTC
	Monistat-3 combination pack (4%, 200 mg, intravaginal cream and 2% external vulvar cream)	Qhs x 3 days and cream bid prn	OTC
	Monistat Dual-Pak (1200 mg ointment based, gelatin ovule and 2% external vulvar cream)	Single dose and cream bid prn	OTC
Terconazole	Terazole-7 0.4% cream (20 mg)	Qhs x 7 days	Rx
	Terazole-3 80 mg supp	Qhs x 3 days	Rx
	Terazole-3 0.8% cream (40 mg)	Qhs x 3 days	Rx
Tioconazole	Vagistat-1 6.5% ointment	Single dose	OTC

2.3 Availability of Proposed Active Ingredient in the United States

Miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (Monistat 1 Combination Pack) has been available OTC since June 2001.

2.4 Important Issues With Pharmacologically Related Products

Until 1990, all topical vaginal antifungal drug products approved by the FDA for VVC were available by prescription only. In 1990, the FDA convened an Advisory Committee meeting to obtain expert opinions on whether treatments for VVC should be made available for OTC use. By unanimous vote, the committee recommended that women who had previously been diagnosed by a physician as having VVC and then developed the same symptoms again at a later date were capable of adequately self-treating their disease with an approved 7-day antifungal regimen.

The treatment duration for vaginal products to treat VVC has evolved since 1990 from 7-days to 3-days to the current one-day treatment. A variety of azole antifungal agents and formulations are approved and marketed as OTC products for treating VVC. See Section 2.2 "Currently Available Treatment for Indications" in this review for a list of approved products and their status as OTC or prescription.

2.5 Presubmission Regulatory Activity

The safety and efficacy of miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream was approved in June 1999 (NDA 20-968) for the treatment of vulvovaginal candidiasis (Monistat® Dual-Pak™). In June 2001 the product was approved for OTC use (NDA 21-308) under the name Monistat® 1 Combination Pack. Later, a prefilled applicator version of the product was also approved (NDA 21-308/S-004 and S-005).

The clinical study included in this submission (Study CA-P-2343) was conducted under IND 37,522. A pre-NDA meeting was held on June 24, 2002 to discuss the proposed protocol for Study CA-P-2343. A summary of selected comments provided by the FDA at the pre-NDA meeting on April 24, 2002, on the protocol submitted August 13, 2002, and on the diary card and instructions submitted October 16, 2002 are as follows:

- A single study may be acceptable to support the proposed change in labeling, as long as the study can achieve a 15% delta under the confidence interval calculation recommended.
- The labeling modification of removing the words "at bedtime" is reasonable, but the sponsor should not label their product with the direction of "use anytime".
- The protocol must describe and control of the level of daytime activity and the number of hours a patient is awake before using the product.
- The inclusion criteria should specify that patients should be active on a daily basis and should anticipate activity within 4 hours of daytime administration.
- Patients who receive intravaginal or systemic antifungal therapy within 7 days of randomization; and women with bacterial vaginosis, should be excluded from the study.
- Patients in the daytime arm must use the product within a certain number of hours after waking.

- The number of diagnosed episodes in the preceding 12 months of VVC and the administered treatment should be recorded in the CRF.
- Patients should be told to refrain from intercourse during the study, and from using intravaginal products, including spermicides.
- Specific activities should be captured in the patient's diary along with directions on how to classify activities into different levels.
- A two-sided 95% confidence interval for the analysis of treatment difference should be used.
- Patients who discontinue from the study should return for the follow-up visit, so as not to minimize the amount of missing data.
- A secondary analysis of efficacy by activity level should also be conducted.
- At least 50% of the evaluable patients should have clinical evidence of moderate severity of VVC at entry, defined as a composite score of 7 (as per the draft Guidance for Instudy "*Vulvovaginal Candidiasis - Developing Antimicrobial Drugs for Treatment*", July 1998).
- At least 20% of the patients enrolled should be able to attain an activity level of vigorous, and 80% of the patients should have an activity level of moderate or higher, for at least one of the specified time intervals in the first 4 hours after drug insertion.

FDA's comments were incorporated into a final protocol, which was submitted to the IND as Serial No. 084 (November 19, 2002). No additional comments were sent from the FDA regarding the protocol.

2.6 Other Relevant Background Information

Miconazole nitrate 1200 mg vaginal insert (ovule) is currently being sold in 17 countries and there have been no withdrawals due to safety concerns.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable. No CMC data was included in this submission.

3.2 Animal Pharmacology/Toxicology

Not applicable. No animal pharmacology/toxicology data was included in this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

- Report of Study CA-P-2343: Volumes 1.2 through 1.5
- Electronic datasets: \\Cdsesub1\n21308\S_009\2004-02-13\crt\datasets\CA-P-2343
- Additional tables:
  \\Cdsesub1\n21308\S_009\2004-08-11 and \\Cdsesub1\n21308\S_009\2004-08-17

4.2 Tables of Clinical Studies

Study	Number of Subjects Enrolled	Study Design	Number of Subjects Evaluable	Clinical Cure	Mycological Cure	Therapeutic Cure
CA-P-2343	573 (279 Daytime and 294 Bedtime)	Randomized, Single-Blind, Active Controlled, Non-inferiority	Intent-to-Treat: 570 (278 Daytime and 292 Bedtime)	70.1% (195/278) Daytime vs. 67.1% (196/292) Bedtime	50.7% (141/278) Daytime vs. 50.7% (141/278) Bedtime	43.5% (121/278) Daytime vs. 35.3% (103/292) Bedtime
			Efficacy Evaluable: 312 (149 Daytime and 163 Bedtime)	74.5% (111/149) Daytime vs. 73.6% (120/163) Bedtime	70.5% (105/149) Daytime vs. 63.8% (104/163) Bedtime	57.5% (86/149) Daytime vs. 50.9% (83/163) Bedtime

4.3 Review Strategy

Study CA-P-2343 was considered a pivotal study.

4.4 Data Quality and Integrity

DSI inspections were not conducted for this NDA. Miconazole nitrate is not a NME, has been studied extensively for VVC in a variety of vaginal formulations, and has a well-characterized safety profile. In addition, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

A 10% random sample of subjects (N=57) enrolled in Study CA-P-2343 was generated by the FDA Statistical Reviewer. The applicant was requested to submit the CRFs for these patients for review. Patient diary cards were not reviewed. The FDA Clinical Reviewer examined the CRFs for inclusion/exclusion criteria, dates of visits, clinical signs and symptoms, concomitant

medications and indications, microbiology findings, and evaluability determinations. The data in the CRFs was compared to the electronic datasets generated by the applicant. The Reviewer found not all submitted CRFs contained microbiology reports from the central laboratory.

The following deviations were noted in the CRFs reviewed:

- Patient 54406 (Bedtime group) did not have a TOC visit, but was **included in the Efficacy Evaluable** and Intent-to-Treat populations as a microbiologic, clinical, and therapeutic failure.
- Patient 58707 (Bedtime group) also did not have a TOC visit, but was **included in the Efficacy Evaluable** and Intent-to-Treat populations as a microbiologic failure/**clinical cure**/therapeutic failure.
- Patient 64208 (Daytime group) had a TOC visit outside the window (Day 35 instead of 21-30), but was included in both the Efficacy Evaluable and Intent-to-Treat populations as a **microbiologic cure**/clinical failure/therapeutic failure.
- Patient 69609 (Daytime group) had clinical symptoms and a positive culture for yeast at the TOC visit and was called a **microbiologic cure**/clinical failure/therapeutic failure.

Despite these discrepancies, all cases identified above where considered therapeutic failures, which was the primary efficacy endpoint, and represented both treatment groups. Therefore, applicant's analyses will be accepted.

4.5 Compliance with Good Clinical Practices

Study CA-P-2343 was conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

The applicant obtained certification from each investigator and sub-investigator who enrolled subjects in Study CA-P-2343. No investigator had any disclosable information to reveal.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Not applicable. No pharmacokinetic data was included in the current NDA submission.

5.2 Pharmacodynamics

Not applicable. No information on pharmacodynamics was included in the current NDA submission.

5.3 Exposure-Response Relationships

Not applicable. No information on exposure-response was included in the current NDA submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Study CA-P-2343 was considered a pivotal efficacy study.

6.1.2 General Discussion of Endpoints

The primary endpoint determined in Study CA-P-2343 was therapeutic cure. The therapeutic cure rate was derived from the clinical and mycological responses at the Test-of-Cure Visit, using the algorithm shown below:

Clinical Response	Mycological Response	Therapeutic Cure Rate
Cure	Cure (no growth)	Cure
Cure	Failure (growth)	Failure
Cure	Missing/not interpretable	Non-evaluable
Failure	Cure (no growth)	Failure
Failure	Failure (growth)	Failure
Failure	Missing/not interpretable	Failure
Non-evaluable	Cure (no growth)	Non-evaluable
Non-evaluable	Failure (growth)	Failure
Non-evaluable	Missing/not interpretable	Failure

The algorithm used in Study CA-P-2343 is identical to the suggested algorithm found in the draft Guidance for Industry *"Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment."* July 1998.

6.1.3 Study Design

This was a multicenter, randomized, investigator-blinded, Phase 3 study of single-dose miconazole nitrate 1200 mg vaginal insert (ovule) in the treatment of VVC in adult, otherwise healthy women. Subjects were randomly assigned to self-administer the ovule either at bedtime (subsequently remaining in bed for at least 30 minutes) or at a subject-determined convenient time during the day (within six hours after arising). Both treatment groups also received a nine-

gram tube of 2% miconazole nitrate external vulvar cream to be applied up to twice daily to the vulvar area, as needed for external symptoms, for a maximum of seven days.

The primary efficacy variable for the study was the therapeutic cure rate. A subject was considered a therapeutic cure only if she was both a clinical and mycological cure at the Test-of-Cure Visit (21 to 30 days following intravaginal administration of study drug). If the upper bound of the 95% two-sided confidence interval for the treatment group difference (Daytime minus Bedtime) was less than or equal to 15%, daytime administration would be considered non-inferior to bedtime administration.

The effect of subject activity level on therapeutic cure was performed as a secondary analysis for subjects assigned to daytime administration. Additional secondary efficacy parameters included vulvovaginal symptomatic relief, clinical cure rates, and mycological cure rates for bedtime and daytime administration.

Clinical Reviewer's Comment: The applicant followed recommendations in the draft Guidance for Industry "Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment."(July 1998) with regard to inclusion/exclusion criteria, timing of evaluation visits, assessments performed, definition of clinical outcome, determination of therapeutic response, and statistical analyses.

6.1.4 Efficacy Findings

The therapeutic cure rates for subjects evaluable for efficacy at the Test-of-Cure Visit were 57.5% (86/149) in the Daytime group and 50.9% (83/163) in the Bedtime group, with a 95% confidence interval of (-4.6%, 18.2%). The lower bound of the 95% confidence interval was greater than -15%; therefore, daytime administration is non-inferior to bedtime administration.

Mycological cure rates were 70.5% (105/149) versus 63.8% (104/163), and clinical cure rates were 74.5% (111/149) versus 73.6% (120/163) for the Daytime and Bedtime groups, in the Efficacy evaluable population, respectively.

Results for the Intent-to-Treat population were lower but consistent with the Efficacy Evaluable population: 43.5% (121/287) in the Daytime group compared to 35.3% (103/292) in the Bedtime group for the therapeutic cure rates [95% CI (0.1%, 16.4%)]; 50.7% (141/278) compared to 44.5% (130/292) for mycological cure rates; and 70.1% (195/278) compared to 67.1% (196/292) for clinical cure rates, respectively. Clinical and mycological response rates were positively, but weakly, correlated in both the Efficacy Evaluable and Intent-to-Treat populations.

The therapeutic cure rates at the Test-of-Cure Visit in the Efficacy Evaluable populations in the Daytime group were not significantly different between subjects with a low activity level (60.5% [26/43]) compared to a high activity level (56.2% [59/105]) ($p = 0.7154$). Therapeutic cure rates were lower in the Intent-to-Treat population, but also were not significantly different between the low and high activity levels (48.8% [39/80] compared to 43.0% [80/186], $p = 0.4212$).

Comparisons between treatment schedules for the Efficacy Evaluable and Intent-to-Treat populations showed no statistically significant difference between the Daytime and Bedtime groups for the estimated time to relief of itching, burning, and irritation, and for all three symptoms combined.

6.1.5 Clinical Microbiology

Clinical Reviewer's Comment: The following information was excerpted from the Microbiology Review by Kalavati Suvarna, Ph.D. filed with this NDA.

Of the 573 patients enrolled in Study CA-P-2343, 308 (daytime, n = 147; bedtime, n = 161) met the inclusion and exclusion criteria and had a Test-of-Cure evaluation. The clinical and mycological outcomes of patients stratified by their baseline pathogen are shown in Table 1. The majority of baseline infections were due to *C. albicans* (daytime arm, n = 135; bedtime arm, n = 143). The percentage of patients with resolution of VVC symptoms and eradication of baseline *C. albicans* was similar in
the two treatment arms (daytime = 62%; bedtime = 55%). Few patients were infected with *Candida* species other than *C. albicans*. The other Candida species included *C. glabrata* (daytime arm, n = 8; bedtime arm, n = 13), *C. krusei* (daytime arm, n = 2; bedtime arm, n = 1), *C. parapsilosis* (daytime arm, n = 2; bedtime arm, n = 1), *C. tropicalis* (daytime arm, n = 0; bedtime arm, n = 2), and *C. dubliniensis* (daytime arm, n = 0; bedtime arm, n = 1). Resolution of VVC symptoms and eradication of baseline yeasts was observed in 4 patients with *C. glabrata* (daytime arm, n = 1; bedtime arm, n = 3), 1 patient with *C. krusei* (daytime arm), and 1 patient with *C. parapsilosis* (bedtime arm).

TABLE 1
Clinical and Mycological Outcome of Patients with VVC
Stratified by Baseline Pathogen

Organism (number of patients)	Clinical and mycological cure	Clinical cure and mycological failure	Clinical failure and mycological cure	Clinical and mycological failure	Clinical failure and mycology not done
Daytime Monistat ovule (1200 mg) + 2% external cream					
C. albicans (n = 135)	84 (62%)	16 (12%)	19 (14%)	15 (11%)[a]	1 (1%)
C. glabrata (n = 8)	1	5	1	1	0
C. krusei (n = 2)	1	1	0	1	0
C. parapsilosis (n = 2)	0	0	2	0	0
Bedtime Monistat ovule (1200 mg) + 2% external cream					
C. albicans (n = 143)	79 (55%)[b]	32 (22%)	19 (13%)[a]	13 (9%)[a]	0
C. glabrata (n = 13)	3	4[a]	1	5	0
C. krusei (n = 1)	0	0	0	1	0
C. parapsilosis (n = 1)	1	0	0	0	0
C. tropicalis (n = 2)	0	0	1	1	0
C. dublinensis (n = 1)	0	1	0	0	0

[a] 1 patient had mixed infection due to *C. albicans* and *C. glabrata*
[b] 2 patient had mixed infections (*C. albicans* + *C. glabrata*, n = 1; *C. albicans* + *C. krusei*, n = 1).

Seven patients (5 in the daytime arm and 2 in the bedtime arm) had new infections at the test-of-cure visit due to a pathogen different from that identified at baseline (Table 2)

TABLE 2
Patients with New Infections in Study CA-P-2343

Patient ID	Treatment arm	Baseline pathogen	New pathogen at test of cure visit
52509	DAYTIME	*C. glabrata*	*C. tropicalis*
61506	DAYTIME	*C. krusei*	*C. parapsilosis*
63406	DAYTIME	*C. albicans*	*C. lusitaniae*
68607	DAYTIME	*C. glabrata*	*C. albicans*
69606	DAYTIME	*C. albicans*	*C. glabrata*
55707	BEDTIME	*C. albicans*	*C. parapsilosis*
57107	BEDTIME	*C. albicans*	*C. glabrata*

Susceptibility testing of isolates collected at baseline and at 21-30 days after initiation of treatment was performed using the NCCLS microbroth dilution method (M27A). Please note that breakpoints for miconazole have not been established. The baseline miconazole MIC values of *C. albicans* and *C. glabrata* isolates from patients who showed resolution of VVC symptoms and those who failed clinically overlapped (Table 3). The number of patients with *Candida* species other than *C. albicans* (*C. krusei, C. parapsilosis,* and *C. tropicalis*) were too small to correlate the baseline miconazole MIC values with clinical outcome. Although changes (increase or decrease) in MIC were noted in pre-treatment and post-treatment isolates, these changes did not correlate with clinical outcome.

TABLE 3
Baseline Miconazole MIC Range for the Different Isolates and Correlation with Clinical Outcome

Pathogen	Miconazole MIC range in μg/ml of isolates from patients with clinical cure (number of isolates)	Miconazole MIC range in μg/ml of isolates from patients with clinical cure from patients with clinical failure (number of isolates)
C. albicans	0.06 – 32.0 (214)	0.06 – 32.0 (64)
C. glabrata	0.06 – 32.0 (13)	1.0 - 32.0 (8)
C. krusei	0.06 – 8.0 (2)	16 (1)
C. parapsilosis	0.12 (1)	4 - 8 (2)
C. tropicalis	- (0)	16 (2)

Baseline miconazole MICs were compared with baseline MICs for fluconazole, clotrimazole, terconazole, and butoconazole against all isolates. The results in Table 4 show that some isolates with high miconazole MIC values (16-32 μg/ml) also showed increase in MIC values for azoles other than miconazole (clotrimazole, terconazole, fluconazole, and/or butoconazole), suggesting cross-resistance between azoles.

TABLE 4
MIC Ranges for Clotrimazole, Terconazole, Fluconazole and Butoconazole Stratified by Baseline Miconazole MIC Values

Miconazole MIC in µg/mL (number of isolates)	Clotrimazole MIC range in µg/mL	Terconazole MIC range in µg/mL	Fluconazole MIC range in µg/mL	Butoconazole MIC range in µg/mL
0.06 (n = 235)	0.06 – 0.25	0.06 – 0.12	0.06 – 16.0	0.06
0.12 (n = 19)	0.06 – 0.5	0.06 – 0.25	0.25 – 4.0	0.06
0.25 (n = 8)	0.12 – 0.5	0.06 – 1.0	0.25 – 1.0	0.06
0.5 (n = 8)	0.25 – 4.0	0.06 – 1.0	0.25 – 16.0	0.06 – 0.25
1.0 (n = 4)	0.5 – 8.0	0.06 – 1.0	1.0 – 16.0	0.06 – 0.12
4.0 (n = 4)	0.12 – 16.0	0.06 – 8.0	0.5 – 8.0	0.06 – 0.5
8.0 (n = 12)	0.5 – 16.0	0.25 – 4.0	1.0 – 64.0[a]	0.12 – 4.0
16 (n = 12)	1.0 – 128.0	0.12 – 128.0	0.5 – 128.0[b]	0.06 – 128.0
32 (n = 10)	2.0 – 16.0	2.0 – 32.0	16.0 – 128.0[c]	0.5 – 32.0

[a] 4 isolates had fluconazole MIC = 64 µg/ml
[b] 7 isolates had fluconazole MIC ≥ 64 µg/ml
[c] 6 isolates had fluconazole MIC ≥ 64 µg/ml

In summary, VVC infection in the majority of patients in the study was due to *C. albicans*. There were few patients with infections due to *Candida* species other than *C. albicans* (*C. krusei*, *C. parapsilosis,* and *C. tropicalis*). There was no correlation between miconazole MIC and clinical outcome. Breakpoints for miconazole have not been established. Some isolates with reduced susceptibility to miconazole also showed reduced susceptibility to azoles other than miconazole (clotrimazole, terconazole, fluconazole and/or butoconazole), suggesting cross-resistance between azoles.

6.1.6 Efficacy Conclusions

Daytime administration of miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (Monistat 1 Combination Pack) for the treatment of vulvovaginal candidiasis (VVC) in otherwise healthy women is non-inferior to bedtime administration.

7 INTEGRATED REVIEW OF SAFETY

For a complete description of the safety data obtained from Study CA-P-2343, see Section 10.1 "Review of Individual Study Reports".

7.1 Methods and Findings

Study CA-P-2343 contains safety information from 570 females between 16 and 76 years of age who received a single miconazole nitrate 1200 mg vaginal ovule (278 randomized to daytime administration and 292 randomized to bedtime administration). The external vaginal cream was

used in addition to the ovule by 61.9% (353/570) of the subjects (64.7% in the Daytime group and 59.2% in the Bedtime group).

7.1.1 Deaths

No deaths occurred.

7.1.2 Other Serious Adverse Events

There were three serious adverse events reported by two subjects in the Bedtime group during the study. One subject in the Bedtime group experienced undifferentiated schizophrenia, and a subject in the Daytime group experienced nausea and vomiting. All events were considered not related or of unlikely relationship to study drug by the applicant and the reviewer.

7.1.3 Dropouts and Other Significant Adverse Events

Of the three (1.1%) subjects in the Daytime group who discontinued from the study due to adverse events, one subject had severe vulvovaginal discomfort that was of highly probable relationship to study drug. Of the seven (2.4%) subjects in the Bedtime group who discontinued study participation due to adverse events, one subject had a rash of moderate severity on her hands, arms, legs, and trunk that was considered by the investigator to be of probable relationship to study drug. All other events that led to subject discontinuation were reported by the investigator (and agreed to by the Reviewer) as unlikely or not related to study drug.

7.1.4 Other Search Strategies

None performed.

7.1.5 Common Adverse Events

In the safety population there were of 143 (51.4%) subjects in the Daytime group, and 140 (47.9%) subjects in the Bedtime group who reported at least one treatment-emergent adverse event during the study.

Specific adverse events that occurred >1% in either treatment arm included: headache (14.4% in the Daytime group and 11.6% in the Bedtime group), vulvovaginal discomfort (3.2% and 3.4%), dysmenorrhea (3.2% and 3.4%), back pain (1.4% and 3.4%), genital pruritus (2.2% and 1.4%), diarrhea (2.2% and 1.7%), insomnia (1.4% and 2.7%), vaginal irritation (1.4% and 0.7%), vaginal discharge (1.1% and 0.3%), , fungal infection (1.8% and 0.7%), sinusitis (1.8% and 1.7%), bacterial vaginitis (1.8% and 1.4%), fungal vaginosis (1.1% and 0%), nasopharyngitis (0.7% and 1.7%), abdominal pain (1.1% and 1.7%), constipation 1.1% and 0%), dyspepsia (1.1% and 1.0%), toothache (1.1% and 0.7%), cough (1.8% and 0.3%), pharyngolaryngeal pain (1.1% and 2.1%), upper respiratory tract congestion (1.1% and 0%), pyrexia (1.1% and 0.3%), myalgia (0% and 1.4%), erythema (1.4% and 1.0%), and excoriation (1.4% and 0%).

7.1.6 Less Common Adverse Events

Most events were mild or moderate in severity. A total of 33 (11.9%) adverse events in the Daytime group and 37 (12.7%) adverse events in the Bedtime group were considered to be severe by the investigator. The most common severe adverse event in both groups was vulvovaginal discomfort (6.1% and 6.2%, respectively).

7.1.7 Laboratory Findings

Routine laboratory testing was not performed during the study.

7.1.8 Vital Signs

Routine testing of vital signs was not performed during the study.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the study.

7.1.10 Immunogenicity

Not applicable. No data on immunogenicity was included in the current NDA submission.

7.1.11 Human Carcinogenicity

Not applicable. No data regarding human carcinogenicity was included in the current NDA submission.

7.1.12 Special Safety Studies

Not applicable. There have been no special safety issues identified with this product.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This product does not have potential for dependence or abuse.

7.1.14 Human Reproduction and Pregnancy Data

Miconazole is in Pregnancy Category "C". Miconazole is absorbed only in trace amounts from the vagina; however it should be used in the first trimester of pregnancy only when it is considered essential to the welfare of the patient. Follow-up data from pregnant patients treated with miconazole cream has not revealed adverse effects or complications in infants born to these women. Since nystatin has been used safely during pregnancy for many years, it may be the

antifungal agent of choice in pregnant patients additional data are available on the safety of miconazole.[2]

7.1.15 Assessment of Effect on Growth

Not applicable. This product does not have potential for growth suppression.

7.1.16 Overdose Experience

Not applicable. This product does not have potential for overdosing.

7.1.17 Postmarketing Experience

Miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (Monistat® Dual-Pack™) has been approved since June 1999. In June 2001 the product was approved for OTC use (Monistat® 1 Combination Pack). No postmarketing issues have been identified to date.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Study CA-P-2383 was the primary source of clinical data. A total 573 subjects were enrolled in the study; 279 were randomized to the Daytime group and 294 were randomized to the Bedtime group. Three subjects were considered nonevaluable for the safety population (one in the Daytime group and two in the Bedtime group). The external vaginal cream was used in addition to the ovule by 61.9% (353/570) of the subjects overall (64.7% in the Daytime group and 59.2% in the Bedtime group).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No other studies, postmarketing data, or literature references were used to evaluate safety.

7.2.3 Adequacy of Overall Clinical Experience

The applicant followed recommendations in the draft Guidance for Industry *"Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment"* (July 1998) with regard to the design of Study CA-P-2343 including the inclusion/exclusion criteria, timing of evaluation visits, assessments performed, definition of clinical outcome, determination of therapeutic response, and statistical analyses.

2 DrugDex® - Drug Evaluations. Miconazole. 2004.

Study CA-P-2383 was adequate to detect a 95% two-sided confidence interval for the difference between treatment arms (daytime minus bedtime administration) with an upper bound of no more than 15% in favor of bedtime administration, which was the primary endpoint of the study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No data on special animal testing was included in the current NDA submission.

In vitro susceptibility testing of fungal isolates collected at baseline and at 21-30 days after initiation of treatment was performed using the NCCLS microbroth dilution method (M27A) and was felt to be adequate (see Section 6.1.5 "Clinical Microbiology" of this review and the Microbiology Review for this NDA conducted by Dr. Kalavati Suvarna).

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing (laboratory parameters, vitals signs, etc), although not performed routinely in Study CA-P-2343, is considered adequate since the product has been previously studied extensively in clinical trials.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetics, including metabolism and drug-drug interactions have been determined previously for miconazole. No new information was submitted with the current NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adverse event profile for vaginal miconazole as well as other topical azole and imidazole antifungal agents has been adequately addressed. There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The data from Study CA-P-2343 is considered to be of acceptable quality and completeness.

7.2.9 Additional Submissions, Including Safety Update

There are no on-going clinical trials with the Monistat 1 Combination Pack, therefore there were no additional safety data weresubmitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the Daytime group, eight (2.9%) adverse events were considered to be of highly probable relationship to study drug by the investigator; four (1.4%) adverse events were considered of probable relationship, and 22 (7.9%) adverse events were considered of possible relationship. In the Bedtime group, six (2.1%) adverse events were considered to be of highly probable relationship to study drug by the investigator; seven (2.4%) adverse events were considered of probable relationship, and 32 (11.0%) adverse events were considered of possible relationship. In both groups, the majority of adverse events with highly probable, probable, or possible relationship to study drug were vulvovaginal discomfort.

Drug-related adverse events observed in this study were consistent with the known safety profile of miconazole nitrate and may have been related to the infection for which the subject was being treated (for example, vulvovaginal discomfort as a symptom of VVC).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Only one clinical study was conducted (Study CA-P-2343); therefore, data were not pooled.

7.4.2 Explorations for Predictive Factors

No exploratory analyses were performed.

7.4.3 Causality Determination

Additional assessments of causality were not performed.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

According to the applicant, the physiochemical properties of the formulation allow the ovule to remain *in situ* for up to 4 days. These properties include the bioadhesive liquid inside the soft gelatin shell and the adhesive properties of the gelatin shell itself. Therefore, theoretically, daytime administration versus bedtime administration should not affect the retention of the product. In the current submission, the applicant has conducted a clinical study that demonstrated the non-inferiority of daytime versus bedtime administration of the ovule, regardless of a woman's activity level.

8.2 Drug-Drug Interactions

Administration of oral or intravenous miconazole with coumarin anticoagulants has previously been shown to produce an enhanced anticoagulant effect. In patients receiving oral anticoagulant therapy, the prothrombin time (PT) or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with miconazole, and should be reassessed periodically during concurrent therapy. Alternatively, an antifungal drug other than an imidazole or triazole, such as nystatin, could be substituted for miconazole.[3]

Since only trace amounts of miconazole are absorbed from the vagina, the potential for a drug interaction between the Monistat 1 Combination Pack and warfarin is unlikely; however, the product is currently labeled such that patients taking coumadin should notify their physician before beginning therapy with the Monistat 1 Combination Pack.

8.3 Special Populations

8.3.1 Efficacy in Special Populations

Therapeutic cure rates observed in Study CA-P-2343 by age (16 to 64 years compared to ≥ 65 years) and race (a comparison of Caucasians, Blacks and Hispanics), and can be found in the Review of Study CA-P-2343 (Section 10.1 of this document). Differences, if any, seen in the efficacy rates between the groups are not considered clinically meaningful. No adjustment to the recommended adult dosing of Monistat 1 Combination Pack are warranted based on age or race.

8.3.2 Safety in Special Populations

Miconazole is Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. It is not known whether miconazole is excreted in human milk.

An evaluation of the safety of Monistat 1 Combination Pack in female subjects by age and race (Caucasians, Blacks, and Hispanics) in Study CA-P-2343 was performed. In the Reviewer's opinion, any differences seen in adverse event rates between younger (16 to 64 years) or older subjects (≥ 65 years) or between Caucasian, Black, and Hispanic patients treated with Monistat 1 Combination Pack are not considered clinically meaningful and do not warrant reporting by age or race in the product labeling. For the individual data tables comparing the incidence rates of adverse events, see the Safety Results section in the Review of Study CA-P-2343 (Section 10.1 of this document).

3 DrugDex® - Drug Evaluations. Miconazole. 2004.

8.4 Pediatrics

No data are available on pediatric patients in the current NDA submission. Study CA-P-2343 was conducted in adult women aged 16 years and older.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was held.

8.6 Literature Review

No literature review was performed or deemed necessary.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan is proposed.

8.8 Other Relevant Materials

No other materials were used in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (together as Monistat 1 Combination Pack) are safe and effective for daytime use for the treatment of vulvovaginal candidiasis in otherwise healthy adult women. Monistat 1 Combination Pack is recommended for approval for this indication.

9.2 Recommendation on Regulatory Action

Monistat 1 Combination Pack consisting of a treatment regimen of a single miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream to be used twice daily for up to 7 days, should be approved for the treatment of vulvovaginal candidiasis in otherwise healthy adult women. The words "at bedtime" regarding administration of the ovule can be removed from the drug packaging.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity or required Phase 4 studies at this time.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Clinical Reviewer's Comment: The following information was excerpted from the Labeling Review by Ms. Arlene Solbek, FDA OTC labeling reviewer in HFD-590, filed with this NDA.

A. Carton and Drug Facts Labeling

These comments apply to both SKUs, unless otherwise noted.

1. Non-prefilled SKU: a flag on the fifth panel which stated "**The Only** 1-Day with External Cream for **Itch Relief**" was removed and the following statement was added "ONE TREATMENT OVULE™ Insert plus External Cream for Itch Relief". This is acceptable.

2. Prefilled SKU: a flag on the fifth panel which stated "Convenient Prefilled Applicator" was removed and the following statement was added "ONE

TREATMENT OVULE™ Insert Prefilled Applicator Plus External Cream for Itch Relief". This is acceptable.

3. Both SKUs: on the fifth panel, the following phrases were added:
   DAY *or* NIGHT
   STAYS IN PLACE
   This is acceptable.

4. Both SKUS: on the principal display panel (PDP) a circle symbol stating "CLINICALLY PROVEN" containing the Ortho Symbol was added. This is acceptable.

5. Both SKUs: on the PDP, the Ortho symbol and a statement of quantity of contents (Net. Wt. 1 OVULE™ Insert + 0.32 oz. (9g) Tube) was added. This is acceptable.

6. Non-prefilled SKU: the tamper-evident feature statement located in a box on the bottom panel the carton reads "DO NOT USE IF **PRINTED** SEALED POUCH OR SEALED VAGINAL INSERT BLISTER IS TORN, OPEN OR INCOMPLETELY SEALED. This is acceptable.

7. Both SKUs: in *Drug Facts* in ***Directions***, the statement for use of the vaginal insert was revised from "with the applicator place the vaginal insert into the vagina at bedtime" to read "with the applicator place the vaginal insert into the vagina." This is acceptable.

8. Non-prefilled SKU: in *Drug Facts* in ***Other information***, the first bulleted statement was revised to read "do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed. This is acceptable except that the sponsor should bold the word "printed" to be consistent with the carton labeling.

9. Non-prefilled SKU: we note that the spacing for the headings *Drug Facts* and *Drug Facts* (continued) as well as the subheadings ***Directions, Other information, Inactive ingredients*** and ***Questions*** need to be revised. Remove the extra space between the "F" and "a" in *Drug Facts*. Remove the extra space between "***Drug Facts***" and "(continued)". Left justify ***Directions***. Remove the extra space between "Other" and "information" in ***Other information***. Remove the extra space between the "I" and "nactive" in ***Inactive ingredients*** and between both words of the subheading. Remove the extra spaces between the "Q" and "uestions?" in ***Questions?***. Delete the space between the third and fourth bulleted statements in **Ask a doctor before use if you have**.

10. Both SKUS: realign "***Purpose***" with the "I" in "Vaginal antifungal".

11. Both SKUs: Add the following "expectation of benefit for 1-day products" bulleted statement under ***Other information*** to read as follow:: "this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

B. Consumer Information Leaflet

12. Prefilled Applicator SKU: in the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable.

13. Non-prefilled SKU: in the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE® Insert, even during your menstrual period." Since this is not the prefilled applicator SKU, the statement should read "Use the OVULE® Insert, even during your menstrual period."

14. Non-prefilled SKU: under **What side effects may occur with Monistat®1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE® Insert is inserted. Since this is not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching or irritation may occur when the OVULE® Insert is inserted."

15. Non-prefilled SKU: under **Other information**, the tamper-evident statement was revised to read "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or vaginal blister is torn, open or incompletely sealed.**" This should be revised to be consistent with carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed)**".

16. Prefilled SKU: in the section **Directions for using the Applicator containing the OVULE™ Insert**, the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture. This is acceptable except that we would recommend "As shown in the picture" to be part of the sentence "Or, you can lie on your back with your knees bent."

17. Non-prefilled SKU: See #15. This also applies to the non-prefilled SKU, direction #5, under **Directions for using the Applicator and the OVULE® Insert**. Also under this section, a new direction (#1) was added to direct consumers in how to open the tamper-evident pouch containing the insert and the

applicator. As a result, the rest of the directions were renumbered. This is acceptable.

18. Both SKUs: the statement in the **Directions** to lie down as soon as possible after inserting the insert to reduce leakage was deleted. This is acceptable since this drug treatment is for day or night use.

19. Both SKUs: in the section **Directions for using the External Vulvar Cream,** the fifth direction was revised from "Repeat steps 2-4, each morning and at bedtime for up to 7 days" to "Repeat steps 2-4, up to two times daily, as needed." This is acceptable.

20. Both SKUs: add the following "expectation of benefit for 1-day products" bulleted statement under ***Other information*** to read as follow:: "this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days." This is to be consistent with carton labeling.

C. Pouch

The pouch labeling was not part of the submission. The sponsor sent the pouch labeling separately. It is acceptable.

9.5 Comments to Applicant

Labeling comments were sent by the FDA to the applicant on August 3, 2004. The FDAs comments and the applicant's response on August 18, 2004 are shown below. Ms. Arlene Solbeck, the FDA OTC labeling reviewer, concluded that the applicant's revised labeling for both the applicator Shelf Keeping Unit (SKU) and nonprefilled applicator SKU are acceptable. No additional changes are necessary for approval.

A. Carton and Drug Facts:

1. Non-prefilled SKU: Bold the word "printed" in the first bulleted statement in ***Other information*** to be consistent with the carton labeling.
Applicant' response: Applicant bolded the word "printed in the first bulleted statement in Other information. This is acceptable.

2. Non-prefilled SKU:
   - Remove the extra space between the "F" and "a" in "*Drug Facts*".

Applicant' response: Applicant removed the extra spaces. This is acceptable.

• Remove the extra space between "Drug Facts" and "(continued)".
Applicant' response: Applicant removed the extra space. This is acceptable.

• Left justify "***Directions***".
Applicant' response: Applicant left justified "***Directions***". This is acceptable.

• Remove the extra space between "Other" and "information" in "***Other information***".
Applicant' response: Applicant removed the extra space. This is acceptable.

• Remove the extra space between the "I" and "nactive" in "***Inactive ingredients***" and between both words of the subheading.
Applicant' response: Applicant removed the extra spaces. This is acceptable.

• Remove the extra spaces between the "Q" and "uestions?" in "***Questions?***"
Applicant' response: Applicant removed the extra spaces. This is acceptable.

• Delete the space between the third and fourth bulleted statements under "***Ask a doctor before use if you have***".
Applicant' response: Applicant removed the extra space. This is acceptable.

3. Both SKUs: Realign the "e" in "***Purpose***" with the last "l" in "Vaginal antifungal".
Applicant' response: Applicant realigned "Purpose" with the "I" in "Vaginal antifungal" for both SKUs as requested. This is acceptable.

4. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."
Applicant' response: Applicant added the "expectation of benefit for 1-day products" to both SKUs as requested. This is acceptable.

B. Consumer Information Leaflet:

5. Non-prefilled SKU: In the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE™ Insert, even during your menstrual period." Since this is not the pre-filled applicator SKU, the statement should read "Use the OVULE™ Insert, even during your menstrual period." Revise this statement.
Applicant' response: Applicant revised the first bulleted statement in the section "**How can I get the best results when treating my infection?**" as requested. This is acceptable.

6. Non-prefilled SKU: Under **What side effects may occur with Monistat® 1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE™ Insert is inserted." Since this in not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching, or irritation may occur when the OVULE™ Insert in inserted."
Applicant' response: Applicant revised the first sentence under "**What side effects may occur with Monistat® 1 Combination Pack?"** as requested. This is acceptable.

7. Both SKUs:

- For the prefilled SKU: **Under Directions for using the Applicator containing the Ovule™ Insert**, the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture." This is acceptable, except we would recommend "As shown in the picture" to be part of the sentence "or, you can lie on your back with your knees bent."
- For the non-prefilled SKU: Revise the same direction. It is direction #5.

Applicant' response: Applicant revised direction #3 for the prefilled SKU and direction #5 for the nonprefilled SKU as requested. This is acceptable.

8. Non-prefilled SKU: Under *Other information*, revise the Tamper-Evident Unit statement to be consistent with the carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed**").
Applicant' response: Applicant revised the Tamper-Evident statement as requested. This is acceptable.

9. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."
Applicant' response: Applicant added the "expectation of benefit statement for 1-day products" to both SKUs as requested. This is acceptable.

10 APPENDICES

10.1 Review of Individual Study Reports

PROTOCOL CA-P-2343
A Multi-Centered, Randomized, Parallel-Group, Investigator-Blinded Study to Compare the Safety and Efficacy of MONISTAT® 1 Combination Pack in Bedtime Versus Daytime Administration

DATE STUDY INITIATED:
December 10, 2002

DATE STUDY COMPLETED:
July 28, 2003

Clinical Reviewer's Comment: All tables in this review, unless otherwise noted, are reproduced from the applicant's Study Report of Study CA-P-2343.

10.1.1 Study Objectives

The primary objective of this study was to determine the safety, efficacy, and therapeutic cure rate of a single dose of a miconazole nitrate 1200 mg vaginal insert (ovule), following bedtime or daytime self-administration, for the treatment of vulvovaginal candidiasis (VVC).

Secondary objectives were to determine the estimated time to vulvovaginal symptomatic relief, mycological cure rates, and clinical cure rates for bedtime and daytime administration. The effect of subject activity level on therapeutic cure was also a secondary objective for the daytime administration group.

10.1.2 Study Design

Study CA-P-2343 was a multicenter, randomized, investigator-blinded, Phase 3 study of single-dose miconazole nitrate 1200 mg vaginal insert (ovule) in the treatment of VVC in adult, otherwise healthy women. Subjects were randomly assigned to self-administer the ovule either at bedtime (subsequently remaining in bed for at least 30 minutes) or at a subject-determined convenient time during the day (within six hours after arising). Both treatment groups also received a nine-gram tube of 2% miconazole nitrate external vulvar cream to be applied up to twice daily to the vulvar area, as needed for external symptoms, for a maximum of seven days.

At the Admission Visit, the presence and severity of vulvovaginal signs and symptoms, mycological laboratory test results (*Trichomonas vaginalis*, and clue cells, and 10% KOH-yeast), and concurrent medications were recorded.

Specimens were collected for Papanicolaou (PAP) smear and cultures were collected for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Candida* species. A medical history was obtained and a complete gynecologic examination, including a urine pregnancy test, was performed. A Daily Diary Card was given to each subject specific to the assigned regimen to record drug use, medical occurrences, and other medications used. Subjects assigned to the daytime administration group were also required to record their daily activities for the first four hours after dosing. At the posttherapy telephone contact (seven to 10 days following the first dose of study drug), the use of the study drug and the return of the Daily Diary Card were confirmed, the type, incidence, and severity of any adverse events were reviewed and recorded, and information regarding any concomitant therapy was obtained. A Test-of-Cure Visit was scheduled 21 to 30 days following intravaginal drug administration to evaluate response to therapy and record any adverse events and/or concomitant medications used. At the Test-of-Cure Visit, a clinical history was recorded, a gynecologic examination was performed, vulvovaginal signs and symptoms were reevaluated, and a specimen was collected for *Candida* culture.

Clinical Reviewer's Comment: The applicant followed recommendations in the draft Guidance for Industry "Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment."(July 1998) with regard to inclusion/exclusion criteria, timing of evaluation visits, assessments performed, definition of clinical outcome, determination of therapeutic response, and statistical analyses.

10.1.3 Study Population

Approximately 520 female subjects (260 subjects per treatment group) with VVC who had signed an IRB-approved Informed Consent Form or Assent Form, and who met all protocol inclusion criteria and exhibited none of the exclusion criteria, were to be randomly assigned to one of the two treatment groups to obtain 168 Efficacy Evaluable subjects per treatment group. A minimum of 20% of subjects assigned to the daytime treatment regimen were to attain a vigorous activity level, and 80% were to obtain a moderate or higher activity level for at least one of the four one-hour time intervals following administration of the ovule.

It was recommended that at least 50% or more of the evaluable subjects were to have clinical evidence of disease of at least moderate severity with a minimum total score of 7 based on the clinical scoring system.

Vulvovaginal signs and symptoms experienced by the subjects were scored using the clinical scoring system described below in Section 10.1.4 ("Inclusion Criteria). Disease severity was determined based on a subject's total score, as defined below:

Severity	Total Score
Mild	2 to 6
Moderate	7 to 12
Severe	≥13

Clinical Reviewer's Comment: The draft Guidance for Industry "Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment." (July 1998) recommends that subjects should have a minimum composite signs/symptoms score equal to 2 and that 50% or more of the evaluable subjects should have clinical evidence of disease of at least moderate severity at entry, defined as having a minimal composite score of 7. Severe disease should be defined as a minimal composite sign/symptom score of 13. The applicant has followed the recommendations of the draft Guidance.

10.1.4 Inclusion Criteria

Subjects who met the following criteria were to be eligible for participation in the study:

1. Females, 12 years of age or older; subjects 12 to 17 years of age were to be at least one year post-menarche;
2. Non-pregnant and non-nursing and willing to remain so while using the study drug; Agreed to sexual abstinence, or if sexually active, agreed to use of an effective method of contraception during the study if not surgically sterilized or at least one year post-menopausal. Effective contraceptive methods were defined as oral contraceptives, intrauterine device, Norplant®, Depo- Provera®, Ortho-Evra® patch, or sterilization of either partner. Condoms or other latex-based products were not to be relied upon for contraception because the external cream formulation might have decomposed the latex in the condom;
3. Agreed to use sanitary protection other than tampons for menses beginning less than seven days from the initial administration of study drug;
4. Reported or exhibited at least one clinical vulvovaginal sign and one vulvovaginal symptom resulting in a total vulvovaginal signs and symptoms score of ≥2 evaluated as indicated below:

	CLINICAL SCORING SYSTEM				
	Vulvovaginal Signs and Symptoms				
SYMPTOMS					**SCORE**
Itching	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Burning	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Irritation	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
SIGNS					
Edema	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Erythema	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Excoriation	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Sum of the scores for each sign and symptom **TOTAL SCORE:**					

Clinical Reviewer's Comment: Disease severity was defined according to the draft Guidance for Industry "Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment."(July

1998) as mild (score 2 to 6), moderate (score 7 to 12), or severe (score ≥13). Any subject having a disease severity score of < 2 should be excluded from the Efficacy Evaluable population.

5. Met laboratory test requirements as follows:
    - Positive 10% KOH slide preparation for budding yeast and/or pseudohyphae;
    - Negative saline wet mount for *T. vaginalis* and clue cells;
    - Positive culture for *C. albicans* or other *Candida* species;
    - Negative test results for *N. gonorrhoeae* and *C. trachomatis*;
    - Papanicolaou (PAP) smear performed at admission within normal limits
    - and revealing no evidence of Human Papilloma Virus (HPV); and
    - Negative urine pregnancy test (CARDS Q.S.® or pregnancy test of equal
    - or greater sensitivity);

    Note: a response of "not applicable" was considered acceptable for the inclusion criteria for *Candida* culture, *N. gonorrhoeae, C. trachomatis* test results and PAP smear results, since a subject could be enrolled in the study with these results pending.

6. Signed the IRB approved Informed Consent Form (subjects 18 years of age or older) agreeing to participate after the study had been fully explained. Subjects aged 12 to 17 years were to have a parent or legal guardian present throughout the consent process. The subject (aged 12 to 17 years) was to sign the IRB approved Assent Form. The parent or legal guardian was to sign both the IRB approved Informed Consent Form and the IRB approved Assent Form; and
7. Were in good general health with normal physical examination findings and no clinically significant conditions.

10.1.5 Exclusion Criteria

Subjects who met any of the following criteria were to be excluded from the study:

1. Used vulvovaginal therapeutics (e.g., antifungals, antimicrobials, hormones), vaginal or cervical contraceptive devices, vaginal lubricants, intravaginal foams, jellies, or ointments, medicated or water douches, or feminine sprays, within seven days of Admission Visit;
2. Had a concurrent episode of vaginal or cervical infection, non-infectious vaginitis, bacterial vaginosis, or cervicitis including but not limited to the pathogens *C. trachomatis, N. gonorrhoeae, T. vaginalis, Herpes simplex,* or HPV;
3. Had a history of sensitivity to the imidazole or triazole class of drugs, or any component of the study drug formulations;
4. Used concurrent systemic antibiotics or coumadin-type anticoagulants;
5. Was under treatment or may have required treatment during the study period for cervical intraepithelial neoplasia (CIN) or cervical carcinoma;
6. Exhibited or was under treatment for genital condylomata (HPV, genital warts, herpes ulcers) within 30 days of Admission Visit;

7. Had a history of alcoholism or drug abuse within the past two years;
8. Experienced frequent yeast infections defined as four or more episodes of symptomatic VVC in the previous 12 months;
9. Used an experimental drug or an experimental device within 30 days of admission into the study;
10. Had known human immunodeficiency virus (HIV) seropositivity or clinical documentation of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC); or
11. Had any vaginal or vulvar conditions which would confound the interpretation of the clinical response.

10.1.6 Study Drug

The Monistat 1 Combination Pack used in this study contained a one-dose vaginal ovule with applicator and a nine-gram tube of miconazole nitrate (2%) external vulvar cream (lot numbers 23D616 and 22D668). The ovule consisted of a soft gelatin shell containing 1200 mg miconazole nitrate as the active ingredient. Inactive ingredients for the ovule included gelatin, glycerin, lecithin, mineral oil, titanium dioxide, and white petrolatum.

Miconazole nitrate (2%) was the active ingredient of the external vulvar cream and was a formulation identical to Monistat 7 Vaginal Cream (NDA 17-450). Inactive ingredients for the external vulvar cream included benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol.

10.1.7 Dosage and Administration

Study drug was to be self-administered intravaginally by all subjects within 48 hours of the Admission Visit. Subjects randomized to bedtime administration were to be instructed to use the ovule at bedtime and were to remain in bed for at least 30 minutes after study drug insertion. Subjects randomized to daytime administration were to be instructed to use the ovule within six hours of arising. Subjects in both regimens were to be instructed to apply a small amount of the miconazole nitrate (2%) external vulvar cream on the skin outside the vagina (vulva), if needed, up to twice daily for a maximum of seven days for external symptom relief.

The study coordinator provided written instructions to the subject on how to use the drug and how to properly complete the Daily Diary Card, in addition to directing subjects to follow instructions within the study drug box. Each subject was to be instructed not to reveal the treatment regimen assignment to the investigator.

Subjects randomized to the daytime group were instructed to record on the diary card the level of activity performed for the following time intervals: 0-1 hour, > 1 to 2 hours, >2 to 3 hours, and >3 to 4 hours after insertion of the ovule. The following examples were given on the diary card for each level of activity to help patients classify their own level of activity:

- **Inactive:** sleeping, sitting, lying down, watching television, reading, meditating, etc.

- **Mild Activity:** light walking , shopping, stretching, bowling, yoga, fishing, showering/hairstyling, washing dishes, cooking, setting the table, ironing, making bed, watering plants, Frisbee, etc.
- **Moderate Activity:** brisk walking, cleaning the house, dancing, moving furniture, kayaking, gardening, golfing, playing with children, caring for children and/or adults, any home repair, ice-skating, horseback riding, jazzercise, vacuuming, mopping, scrubbing floor/tub, weight lifting, bicycling (less than 11.9 mph), mowing lawn, raking leaves, painting, carpentry, shoveling snow, etc.
- **Vigorous Activity:** aerobics, tennis, bicycling (greater than 11.9 mph), circuit training, rowing, rock climbing, skiing, snowmobiling, running/jogging, stair climbing, carrying groceries upstairs, squash, hiking, backpacking, swimming, etc.

Subjects were to refrain from intercourse or use of any intravaginal products for the duration of the study. If any medical procedures were planned (e.g., dental work) where prophylactic antibiotic treatment was anticipated, subjects were to postpone the procedure(s) for the length of the study or were to refrain from enrollment in the study. Subjects were also to agree to use sanitary protection other than tampons in case of menses for at least seven days after the intravaginal application of the study drug.

Subjects were to inform the investigator if symptoms worsened or did not improve within three days of study drug administration. An interim visit was to be scheduled, if appropriate.

10.1.8 Treatment Compliance

Each subject was to record use of study drug on the Daily Diary Card. A subject was to be considered compliant if she self-administered the ovule within 48 hours of the Admission Visit and during the timeline established by the assigned regimen (at bedtime, remaining in bed for at least 30 minutes for subjects randomized to bedtime administration, or within six hours of arising for subjects randomized to daytime administration). Use of the external vulvar cream was not required for a subject to be considered compliant.

10.1.9 Concomitant Therapy

Concomitant medications other than those listed in the exclusion criteria were permitted during the study. All medications other than study drug were to be recorded in the source document and on the Concomitant Medications page of the CRF. The investigator was to inform the study monitor if the use of any new medications was deemed necessary.

10.1.10 Overview of Study Procedures

Figure 1 provides an overview of the timing of procedures performed during the study.

FIGURE 1
Time and Events Schedule

Procedure	Admission Visit		On-study Procedures	Post Treatment Contact	Optional Interim Visit[a]	Test-of-Cure Visit/ Discontinuation
Study Day	0	1	2-7[b]	7-10[b]		21-30[b]
Informed consent obtained	X					
Inclusion/exclusion criteria reviewed	X					
Tests for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and pregnancy	X					
Pertinent medical history and physical examination	X				X	
Gynecologic exam	X				X	X
PAP smear	X				X[c]	
KOH and wet mount laboratory tests	X				X[c]	
Evaluation of vulvovaginal signs and symptoms and determination of clinical score	X				X	X
Collect and ship vaginal culture samples	X				X	X
Review and confirm therapy dates				X		
Randomization, dispense study drug and Daily Diary Card	X					
Instruct subject on study drug usage, completion of Daily Diary Card, and return of used/unused study drug packaging	X					
Study drug administration - MONISTAT® 1 OVULE™ Insert		X[d]				
Study drug administration - external vulvar cream (as needed)		X	X			
Complete Daily Diary Card		X	X	X		
Collect and review completed Daily Diary Card				X	X	X
Collect used and unused study drug					X[c]	X
Complete case report form(s)	X			X	X	X
Review concurrent medications	X			X	X	X
Document adverse events		X	X	X	X	X

[a] If a subject was discontinued at the optional interim visit, all procedures scheduled for the 21-30 day Test-of-Cure Visit were to be performed.
[b] Study day was based on day of study drug administration.
[c] Procedure was to be conducted at the optional interim visit, at the discretion of the investigator.
[d] Study drug must have been used within 48 hours of randomization on Day 0. Study drug administration was on Day 1. For subjects randomly assigned to bedtime administration, Day 0 and Day 1 may have been the same.

10.1.11 Admission Visit

At the Admission Visit, prior to dispensing of study drug, all subjects were to be evaluated by the investigator. The following procedures/assessments were performed:

- Relevant medical, gynecological, and vaginitis history
- A complete physical (including height, weight, blood pressure, and pulse)
- A complete gynecologic examination (including PAP smear and urine pregnancy test)
- Vulvovaginal signs and symptoms assessment

For eligibility, each subject was to have the following documented:

- PAP smear at the Admission Visit, showing no evidence of HPV or clinically significant abnormal findings;
- Positive 10% KOH preparation for budding yeast and/or pseudohyphae;
- Negative saline wet mount for *T. vaginalis* and clue cells;
- Positive culture for *C. albicans* or other *Candida* species;
- Negative test results for *N. gonorrhoeae* and for *C. trachomatis*; and
- Negative urine pregnancy test (———— ® or pregnancy test of equal or greater sensitivity).

10.1.12 Post-Therapy Telephone Contact

The site coordinator was to perform a posttherapy telephone contact approximately seven to 10 days following administration of the ovule. During this contact, the site coordinator was to:

- Ensure subject compliance with the protocol;
- Evaluate the subject's response to therapy;
- Confirm the use of the study drug; and
- Inquire about any adverse events or concomitant medications.
- If adverse events were reported, the site coordinator was to refer the subject to the investigator to determine if an interim visit was required, and the appropriate follow-up treatment. Information from the telephone contact was to be recorded in the source document and on the CRF.

10.1.13 Optional Interim Visit

If the subject reported no improvement, or worsening of symptoms within three days of ovule administration, or the subject's response to therapy was considered inadequate during the telephone contact, an interim office visit was to be scheduled. The investigator was to remain blinded to treatment regimen, perform a full evaluation, and determine if the subject should be discontinued from the study. If discontinuation was necessary, all procedures scheduled for the 21 to 30 day Test-of-Cure Visit were to be performed. Information from the interim visit was to be recorded in the source document and on the CRF.

10.1.14 Test-of-Cure Visit

A Test-of-Cure Visit was to be scheduled 21 to 30 days after intravaginal study drug administration on Day 1. If the subject returned prior to 21 days after initial intravaginal study drug administration, then the subject was to be instructed to return within the indicated time frame. The following procedures were to be performed at this visit:

- Record clinical history, adverse events, and concomitant medications;
- Perform a gynecological examination (speculum);
- Perform a vulvovaginal signs and symptoms assessment and determine the
- clinical score;
- Obtain specimen for MIC and *Candida* culture; and

- Collect the Daily Diary Card (if not previously returned), the drug packaging, and any used and unused study drug.

10.1.15 Discontinuation from the Study

Subjects who were randomized could be discontinued from the study at any time for the following reasons:

- Clinically significant adverse event(s);
- Subject request;
- No response to therapy including incomplete resolution of signs and symptoms, or need for additional vulvovaginal or systemic treatment in the investigator's clinical judgment; or
- Investigator's discretion.

Upon discontinuation of a subject from the study, the investigator was to perform the procedures required at the Test-of-Cure Visit.

10.1.16 Efficacy Evaluations

The primary efficacy variable for the study was the therapeutic cure rate, which combined clinical and mycological responses at the Test-of-Cure Visit in the Efficacy Evaluable population. A subject was to be considered a therapeutic cure if she was both a clinical and mycological cure at the Test-of-Cure Visit.

Clinical Response: The definition of clinical cure was based upon the improvement or absence of vulvovaginal signs and symptoms of VVC from Admission to the Test-of-Cure Visit. To be considered a clinical cure, any sign or symptom with a score of one (mild) or two (moderate) at Admission was to be zero (absent) at the Test-of-Cure Visit, and any sign or symptom with a score of three (severe) at Admission was to be zero or one. All signs and symptoms had to satisfy these criteria for a clinical response to be considered a cure. If these criteria were not met, the clinical response was "failure". If the result of evaluation of any sign or symptom was unknown, the clinical response was "non-evaluable."

Mycological Response: A mycological cure was indicated if the culture for any fungal species was positive at Admission and negative at the Test-of-Cure Visit. If the fungal culture was positive at the Test-of-Cure Visit, the mycological response was "failure".

Therapeutic Cure Rate: The therapeutic cure rate was derived from the clinical and mycological responses at the Test-of-Cure Visit, using the algorithm shown below:

Clinical Response	Mycological Response	Therapeutic Cure Rate
Cure	Cure (no growth)	Cure
Cure	Failure (growth)	Failure
Cure	Missing/not interpretable	Non-evaluable
Failure	Cure (no growth)	Failure
Failure	Failure (growth)	Failure
Failure	Missing/not interpretable	Failure
Non-evaluable	Cure (no growth)	Non-evaluable
Non-evaluable	Failure (growth)	Failure
Non-evaluable	Missing/not interpretable	Failure

Vulvovaginal Symptomatic Relief: Vulvovaginal symptomatic relief was defined as the reduction of all vulvovaginal symptoms reported at Admission to absent (0) up to Day 7 on the subject Daily Diary Card. Days to Initial Relief, as described in the Statistical Analysis Plan, was changed to Estimated Time to Initial Relief, in order to more precisely define the time point of the first occurrence of vulvovaginal symptom relief in relationship to the time of ovule insertion. Each Diary Day was converted to an estimated hour, starting with the ovule insertion time (am or pm). Estimated 12-hour intervals were assigned to each Diary Day according to the following algorithm:

Estimated Time Intervals

Diary Time	Daytime	Bedtime
30 min	30 min	30 min
2 am	24 hr	12 hr
2 pm	36 hr	24 hr
3 am	48 hr	36 hr
3 pm	60 hr	48 hr
4 am	72 hr	60 hr
4 pm	84 hr	72 hr
5 am	96 hr	84 hr
5 pm	108 hr	96 hr
6 am	120 hr	108 hr
6 pm	132 hr	120 hr
7 am	144 hr	132 hr
7 pm	156 hr	144 hr

Estimated time to initial relief of vulvovaginal itching, burning, and irritation were calculated for each symptom separately by taking the difference between the first time point the symptom was relieved and the time of ovule insertion.

10.1.17 Safety Evaluations

Treatment-emergent adverse events included any unfavorable and unintended sign, symptom, or disease associated with the use of study drug, regardless of relationship to study drug. During the post-therapy telephone contact, optional interim visit, or at the Test-of-Cure Visit, any new or continuing adverse events not present at the Admission Visit were to be recorded; deterioration of a medical condition present at the Admission Visit was recorded as a new adverse event. Any medical condition at baseline, which remained unchanged or improved, was not recorded as an adverse event. All adverse events were recorded in the source document and on the CRF.

All adverse events were to be followed to resolution or until a stable clinical condition was achieved. All procedures required for the management of the adverse event and the ultimate outcome of the event were recorded. If a pregnancy occurred during the study, study drug was to be discontinued immediately and the medical monitor was to be notified. Follow-up information regarding the outcome of a pregnancy and any postnatal sequelae in the infant was to be obtained.

Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), where an included term was the description most closely related to the investigator's response, the preferred term was a group of closely related included terms, and the body system was a broad category including related preferred terms. The investigator assigned a relationship to study drug for each treatment emergent adverse event (i.e., not related, unlikely, possible, probable, highly probable).

The severity of an adverse event was a qualitative assessment of the degree of intensity as determined by the investigator or reported by the subject. The assessment of severity (mild, moderate, or severe) was made irrespective of drug relationship or seriousness of the event.

A serious adverse event included any event that was fatal or life threatening, was permanently disabling, required or prolonged hospitalization, or was a congenital anomaly or birth defect. The subject was to be followed until the condition resolved and the etiology identified.

10.1.18 Sample Size Determination

The sample size for the study was based on the primary efficacy variable of therapeutic cure. Assuming a therapeutic cure rate of 60%, the applicant determined (using the method of Blackwelder) approximately 168 evaluable subjects were required per treatment arm to demonstrate non-inferiority between the two treatment groups. This determination assumed a 95% two-sided confidence interval for the difference between treatment arms with an upper bound of no more than 15% in favor of bedtime administration and a statistical power of 80%. Allowing for a nonevaluable proportion of approximately 35%, approximately 260 subjects were enrolled in each treatment arm.

10.1.19 Analysis Populations

Safety Evaluable Population: To be evaluable for safety, a subject must have used study drug (ovule or external vulvar cream) and relayed safety information to the investigator through the Daily Diary Card, the telephone contact, or at the Test-of-Cure Visit.

Subjects who reported adverse event information but failed to return the Daily Diary Card were presumed to have taken study drug, and therefore were to be considered evaluable for safety. A list of subjects excluded from the analysis of safety and reasons for exclusion was provided by the applicant.

Intent-to-Treat Population: The Intent-to-Treat population consisted of all subjects who used study drug (ovule or external vulvar cream). Subjects who were discontinued were considered treatment failures but were evaluated in all populations for all analyses. Subjects with missing outcome data were considered to have the worst-case scenario outcome and were classified as having a response of clinical failure/mycological persistence (failure).

Efficacy Evaluable Population: The primary efficacy analysis was based on the Efficacy Evaluable population. Subjects who met any of the following criteria were excluded from the efficacy analysis (in decreasing hierarchical order by primary reason for exclusion):

- Did not use study drug as reported on the Daily Diary Card or via the post-therapy telephone contact;
- Were lost to follow-up after the Admission Visit;
- Had a total vulvovaginal signs and symptoms severity score at admission of <2;
- Had a missing or negative culture for *Candida* at Admission ($\geq +1$ growth on culture was considered positive);
- Had a positive or missing test at admission for *C. trachomatis* and/or *N. gonorrhoeae*;
- Used study drug incorrectly: subjects were to use the ovule once, either at bedtime (remaining in bed for at least 30 minutes) or during the day (within 6 hours of arising) and within 48 hours of the Admission Visit;
- Used systemic antibiotics, or systemic or vaginal antifungals; if the subject required additional vulvovaginal or systemic antifungal therapy and the clinical response was considered failure, then the subject was evaluable for efficacy. Note: if the subject required additional vulvovaginal or systemic antifungal therapy and did not withdraw from the study, then their interim visit was used as the Test-of-Cure Visit for clinical response and mycological response; these subjects were considered failures and were evaluable for efficacy.
- Had the Test-of-Cure Visit prior to Day 21 or after Day 30. If the subject had a response of therapeutic failure but conformed to the drug use requirements, the subject was evaluable;
- Had missing clinical or mycological data at the Test-of-Cure Visit so the therapeutic response could not be defined;
- Did not meet all inclusion criteria, or met one or more exclusion criteria Note: subjects who had a hysterectomy and did not have an admission pregnancy test were evaluable.

- Developed other vulvovaginal infection after admission; or
- Had a Pap smear taken at admission indicative of HPV, precancerous lesions, or carcinoma *in situ*.

10.1.20 Primary and Secondary Efficacy Analyses

If the upper bound of the 95% two-sided confidence interval for the treatment group difference in therapeutic cure (Daytime minus Bedtime) was less than or equal to 15%, daytime administration would be considered non-inferior to bedtime administration.

A secondary efficacy analysis was performed on therapeutic cure and the effect of the subject's activity level for the Daytime group. Each subject assigned to the daytime regimen was classified into the high or low activity level based on the hourly self-evaluations made during the first four hours following treatment administration. Subjects having an activity assessment of moderate or vigorous at any of the four hourly evaluations were to be classified as high activity level; all other subjects were to be classified as low activity level. The relationship of activity level to therapeutic cure was to be determined using Fisher's exact test. If a subject had more than one response to for an activity level for the same time interval, then the maximum activity level was used in the analysis.

Further secondary analyses included the outcomes for clinical and mycological cure rates individually.

Vulvovaginal symptomatic relief was defined as the reduction of all vulvovaginal symptoms present at the Admission Visit reported as absent (0) up to day seven on the subject Daily Diary Card. Estimated time to initial relief of vulvovaginal itching, burning, and irritation was to be determined for each individual symptom by calculating the difference between the first time point of symptom relief and the time of ovule insertion. Each Diary Day was converted to an estimated 12-hour interval, starting with ovule insertion time (am or pm). Estimated time to initial relief was defined as the number of hours to the first occurrence of relief; missing values were calculated as nonrelief. Subjects who were asymptomatic at both Admission and Day 7 for one of these parameters were to be classified as "Reported No Itching at Admission and Day 7," "Reported No Burning at Admission and Day 7," or "Reported No Irritation at Admission and Day 7". If Day 1 (prior to intravaginal ovule insertion) data were missing on the Daily Diary Card, then Day 0 (Admission CRF) data were to be used for calculation of estimated time to initial relief. If all non-Day 1 (prior to intravaginal ovule insertion) Diary data was missing, then the subject's data were to be censored (never experienced relief). In addition, the change in each clinical vulvovaginal sign and symptom was to be analyzed using the one-degree of freedom Cochran-Mantel-Haenszel test.

There was no adjustment for multiple endpoints.

10.1.21 Safety Analyses

All safety analyses were based on the safety evaluable population. The safety analyses were to examine the incidence, severity (mild, moderate, or severe), relationship to therapy (not related, unlikely, possible, probable, or highly probable), and type of adverse event reported by subject from the insertion date of study drug through the Test-of-Cure Visit. The proportion of subjects reporting at least one adverse event and the proportion of subjects experiencing each type of adverse event were to be summarized for each treatment group.

10.1.22 Deviations from the Proposed Analysis

Thirteen women in the Daytime group and 12 women in the Bedtime group with hysterectomies were included in the Efficacy Evaluable population by the applicant although a urine pregnancy test was not performed at Admission. Seven subjects (51408, 55807, 58407, 58409, 61309, 65909 and 69209) in the Daytime group and seven subjects (53708, 54609, 58209, 58309, 62508, 63909, and 69906) in the Bedtime group were included by the applicant in the Efficacy Evaluable population with the Test-of-Cure Visit occurring within ±10% of the 21 to 30 days allowed by the protocol.

Clinical Reviewer's Comment: These deviations from the protocol are not considered clinically significant and the Reviewer agrees with the applicant that these patients may remain in the Efficacy Evaluable population.

Nine subjects (50106, 53508, 54707, 56208, 56407, 56408, 57506, 57507, and 66109) randomized to the Daytime group received the incorrect (Bedtime) Daily Diary. Five subjects (53506, 57406, 60206, 60208, and 64707) randomized to the Bedtime group received the incorrect (Daytime) Daily Diary. Subjects were included and analyzed in the group corresponding to the actual time of study drug use by the applicant.

Clinical Reviewer's Comment: The FDA Statistical and Clinical Reviewers analyzed the subjects by treatment group they were randomized to and not by the actual time of study drug use. The results of this analysis can be found in "Efficacy Results," Section 10.1.24.

10.1.23 Enrollment and Evaluability

A total 573 subjects were enrolled; 279 were randomized to the Daytime group and 294 were randomized to the Bedtime group. Three subjects were considered nonevaluable for the safety, Intent-to-Treat, or Efficacy Evaluable populations; two subjects (54806 in the Daytime group and 61106 in the Bedtime group) were lost to follow-up, did not return a Daily Diary Card, and had no record of treatment for either the ovule or external cream, and one subject (61906 in the Bedtime group) was randomized, but did not take drug. Therefore, there were 570 subjects in both the safety and Intent-to-Treat populations (278 in the Daytime group and 292 in the Bedtime group).

A less than half of the subjects in the safety and Intent-to-Treat populations were nonevaluable for efficacy and were excluded from the Efficacy Evaluable population in each treatment group (46.6% and 44.6%, respectively). Reasons for inevaluability are shown in Table 1.

Clinical Reviewer's Comment: A summary of screening failures (N=229) is presented below. Note: a subject could have had more than one reason for failing screening.

Negative KOH = 164
Positive Wet Mount = 73
Insufficient vulvovaginal signs and symptoms = 34
Failed other inclusion/exclusion criteria = 19
Frequent yeast (>4 within 12 months) = 6
Prohibited medications = 5
Pregnancy = 1
Withdrew consent = 1

Clinical Reviewer's Comment: Table 1 was adapted for clarity by the reviewer from Table 3 in the applicant's study report.

TABLE 1
Evaluability for Safety, Intent-to-Treat, and Efficacy Evaluable Populations

	Daytime	**Bedtime**
Enrolled	279	294
Safety[a] Population and Intent-to-Treat Population	278 (99.6%)	292 (99.3%)
Did not take study drug or study drug usage not confirmed	*1*	*2*
Efficacy Evaluable Population	149 (53.4%)	163 (55.4%)
Lost to follow-up	*7*	*5*
Negative or missing admission culture	*70*	*84*
Positive or missing culture for C. trachomatis or N. gonorrhoeae	*1*	*3*
Study drug used incorrectly	*19*	*7*
Use of systemic antimicrobials or antifungals	*12*	*12*
TOC visit outside of window (Before Day 21 or after Day 30)[b]	*9*	*2*
Missing clinical or mycological data at TOC	*1*	*1*
Inclusion/exclusion criteria violation	*4*	*6*
Developed other VV infection after admission	*3*	*3*
Pap smear with HPV, precancerous lesion, or carcinoma in-situ	*3*	*5*

[a] Subjects who reported adverse event information but failed to return a diary card to indicate study drug usage were presumed to have taken study drug and therefore were evaluable for safety.
[b] Subjects who presented for their Test-of-Cure Visit within ±10% of the allotted Test-of-Cure window were included in the analysis.
NOTE: Percentages are based on the number of subjects enrolled in each treatment group.

Clinical Comment: Selected reasons for exclusion from the Efficacy Evaluable population were investigated by the Reviewer to try and obtain additional information about why subjects were thought to be unevaluable by the applicant. The additional information was found in Appendix 3.7 "Comments noted on Case Report Forms" of the applicant's study report and is summarized below. In many instances alternative reasons for exclusion were noted in addition to the primary reason. Regardless of the reason for exclusion, the Reviewer agrees with the applicant that all patients listed below should not be included in the Efficacy Evaluable population.

Study Drug Used Incorrectly
More subjects in the Daytime group than in the Bedtime group were classified as "study drug used incorrectly" (19 versus 7). The individual subjects and the reasons noted on the CRF are listed below. Many subjects did not follow instructions regarding when to insert the ovule or did not return a diary card to document drug administration.

Daytime
50806: inserted at bedtime
52107: inserted in afternoon instead of waiting until the following morning
52109: inserted in the evening instead of waiting until the following morning
53606: did not insert within 48 hours
53609: no admission PAP
53706: no explanation provided on CRF
54009: did not insert within 48 hours
55708: inserted in afternoon instead of waiting until the following morning
56609: did not insert within 6 hours of awakening
56707: did not insert within 6 hours of awakening
57006: admission PAP specimen was inadequate; lost to follow-up
57308: page 1 of diary not returned
60106: increased burning noted by subject; used additional antifungal treatment - terconazole
60506: may have inserted in morning instead of bedtime
61508: subject withdrew consent
61808: inserted in afternoon instead of waiting until the following morning
62307: no diary returned; lost to follow-up
64308: no admission PAP
64608: no diary returned; lost to follow-up

Bedtime
56308: lost to follow-up
57406: subject was given a Daytime diary although randomized to Bedtime use; TOC visit occurred after Day 30
58608: lost to follow-up
60409: may have inserted in the morning instead of at bedtime
62306: did not remain in bed for 30 minutes after insertion
63408: may not have remained in bed for 30 minutes after insertion
63707: ovule fell into the toilet while subject was trying to insert it; used cream only

Inclusion/Exclusion Criteria Violation
Ten patients total (4 versus 6) were noted to have "inclusion/exclusion criteria violation" as the reasons for unevaluability. The exact criterion that was in violation is noted below.

Daytime
54307: no VVC signs noted on admission
58908: used systemic antimicrobial within 2 days of admission
62308: no VVC signs noted on admission
68306: reason for violation not noted

Bedtime
50409: admission culture positive for BV
55808: found ovule in bed; withdrew consent; insufficient VVC signs for inclusion

56708: no VVC signs noted on admission
58207: reason for violation not noted
59309: no VVC signs noted on admission
62707: admission culture positive for BV

Lost to Follow up
In addition to subjects not returning for follow-up visits, four of the 7 subjects in the Daytime group and 3 of the 5 in the Bedtime group had additional reasons for exclusion:

Daytime
54906: admission culture negative
55809: admission culture negative
61109: admission culture negative
65706: admission culture negative

Bedtime
50207: admission culture positive for BV
54308: no clue cells seen on admission
56309: admission culture negative

Four subjects, two in each group (66608 and 61107 in the Daytime group and 51407 and 65407 in the Bedtime group), used tampons in the first seven days of the study.

Clinical Reviewer's Comment: According to draft Guidance for Industry "Vulvovaginal Candidiasis – Developing Antimicrobial Drugs for Treatment." (July 1998) these patients should be excluded from the evaluable population along with those patients who used other vaginal products (douche, N-9 products, condoms etc.) during the first 7 days following drug administration.

The protocol stated that subjects were to refrain from intercourse or use of any intravaginal products for the duration of the study and that subjects must agree to use sanitary protection other than tampons for menses beginning less than 7 days from the initial administration of study drug.

Four subjects used a tampon within 7 days of administration of study drug. The applicant noted these patients as protocol deviations, but did not exclude them from the Efficacy Evaluable population for this reason, although, two of the four patients were excluded for other reasons. One subject in the Daytime group (failure) and one subject in the Bedtime group (cure) were considered evaluable.

Using the "pertinent history" dataset provided by the applicant, two evaluable subjects in the Daytime group (1 failure) and four evaluable subjects in the Bedtime group (2 failures) were found to have used douche or feminine spray, tampons, or a vulvovaginal therapeutic at some point during the study although the timing of use in relation to study drug administration is not

reported. In the "subject diary" dataset, 6 evaluable subjects in the Daytime group (4 cures) and 8 evaluable subjects in the Bedtime group (4 cures) were found to have used at least one other vulvovaginal product during the first 7 days of the study. These products included: spermacide, feminine wash, sanitary pad, KY jelly, and antibacterial wipe. The 14 subjects identified in the "subject diary" dataset includes 4 of the subjects found in the medication history dataset (N=18 patients total). In addition to these 18 subjects, many other subjects reported intercourse using condoms during the study (timing of use in relation to study drug administration is not reported).

Removing all 18 subjects who used tampons or other vaginal products from the Efficacy Evaluable population (7 subjects in the Daytime group (5 cures) and 11 subjects in the Bedtime group (5 cures)), results in a therapeutic cure rate of (57% (81/142) for the Daytime group and 51% (78/152) for the Bedtime group, which does not change the overall results.

Enrollment by Study Site

Fifty-three investigators enrolled subjects into the study, as shown in Table 2. Seven investigators enrolled ≥ 10 subjects in each group [redacted], [redacted]). Four investigators ([redacted]) did not enroll any subjects in the Daytime group, and four investigators ([redacted]) did not enroll any subjects in the Bedtime group.

Clinical Reviewer's Comment: An analysis of therapeutic cure by study site was conducted by the applicant. However, the results are not included here since no site enrolled more than 10% of the total study population and therefore an individual site has little potential to affect the overall study results.

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TABLE 2
Number and Percent of Subjects Analyzed in the Safety, Intent-to-Treat, and Efficacy Evaluable Populations by Investigator: All Subjects Enrolled

	Daytime MONISTAT 1							Bedtime MONISTAT 1						
		Number Analyzed							Number Analyzed					
	Number Enrolled	Safety		Intent-to Treat		Efficacy		Number Enrolled	Safety		Intent-to Treat		Efficacy	
Investigator	N	n	(%)	n	(%)	n	(%)	N	n	(%)	n	(%)	n	(%)
	6	6	(100.0)	6	(100.0)	5	(83.3)	5	5	(100.0)	5	(100.0)	3	(60.0)
	9	9	(100.0)	9	(100.0)	4	(44.4)	9	9	(100.0)	9	(100.0)	4	(44.4)
	3	3	(100.0)	3	(100.0)	0	(0.0)	0	0	0	0			
	5	5	(100.0)	5	(100.0)	2	(40.0)	5	5	(100.0)	5	(100.0)	2	(40.0)
	4	4	(100.0)	4	(100.0)	1	(25.0)	3	3	(100.0)	3	(100.0)	1	(33.3)
	2	2	(100.0)	2	(100.0)	0	(0.0)	3	3	(100.0)	3	(100.0)	0	(0.0)
	7	7	(100.0)	7	(100.0)	2	(28.6)	7	7	(100.0)	7	(100.0)	3	(42.9)
	2	2	(100.0)	2	(100.0)	1	(50.0)	4	4	(100.0)	4	(100.0)	0	(0.0)
	6	6	(100.0)	6	(100.0)	2	(33.3)	7	7	(100.0)	7	(100.0)	4	(57.1)
	1	1	(100.0)	1	(100.0)	0	(0.0)	2	2	(100.0)	2	(100.0)	2	(100.0)
	5	5	(100.0)	5	(100.0)	1	(20.0)	6	6	(100.0)	6	(100.0)	3	(50.0)
	0	0		0		0		2	2	(100.0)	2	(100.0)	2	(100.0)
	4	4	(100.0)	4	(100.0)	1	(25.0)	4	4	(100.0)	4	(100.0)	2	(50.0)
	2	2	(100.0)	2	(100.0)	1	(50.0)	2	2	(100.0)	2	(100.0)	2	(100.0)
	13	13	(100.0)	13	(100.0)	12	(92.3)	12	12	(100.0)	12	(100.0)	7	(58.3)
	5	5	(100.0)	5	(100.0)	4	(80.0)	6	6	(100.0)	6	(100.0)	3	(50.0)
	2	1	(50.0)	1	(50.0)	1	(50.0)	3	3	(100.0)	3	(100.0)	2	(66.7)
	9	9	(100.0)	9	(100.0)	7	(77.8)	7	7	(100.0)	7	(100.0)	4	(57.1)
	0	0		0		0		2	2	(100.0)	2	(100.0)	2	(100.0)
	12	12	(100.0)	12	(100.0)	7	(58.3)	11	11	(100.0)	11	(100.0)	6	(54.5)
	3	3	(100.0)	3	(100.0)	0	(0.0)	4	4	(100.0)	4	(100.0)	3	(75.0)
	3	3	(100.0)	3	(100.0)	2	(66.7)	6	6	(100.0)	6	(100.0)	2	(33.3)
	2	2	(100.0)	2	(100.0)	0	(0.0)	1	1	(100.0)	1	(100.0)	0	(0.0)
	5	5	(100.0)	5	(100.0)	3	(60.0)	5	5	(100.0)	5	(100.0)	2	(40.0)
	4	4	(100.0)	4	(100.0)	2	(50.0)	5	5	(100.0)	5	(100.0)	1	(20.0)
	3	3	(100.0)	3	(100.0)	2	(66.7)	4	4	(100.0)	4	(100.0)	3	(75.0)
	22	22	(100.0)	22	(100.0)	18	(81.8)	23	23	(100.0)	23	(100.0)	23	(100.0)
	4	4	(100.0)	4	(100.0)	3	(75.0)	4	4	(100.0)	4	(100.0)	4	(100.0)
	10	10	(100.0)	10	(100.0)	6	(60.0)	10	10	(100.0)	10	(100.0)	6	(60.0)
	2	2	(100.0)	2	(100.0)	0	(0.0)	3	3	(100.0)	3	(100.0)	1	(33.3)
	5	5	(100.0)	5	(100.0)	3	(60.0)	4	4	(100.0)	4	(100.0)	3	(75.0)
	2	2	(100.0)	2	(100.0)	2	(100.0)	1	1	(100.0)	1	(100.0)	1	(100.0)
	4	4	(100.0)	4	(100.0)	2	(50.0)	4	4	(100.0)	4	(100.0)	0	(0.0)
	5	5	(100.0)	5	(100.0)	1	(20.0)	4	4	(100.0)	4	(100.0)	0	(0.0)
	1	1	(100.0)	1	(100.0)	0	(0.0)	0	0		0		0	
	4	4	(100.0)	4	(100.0)	0	(0.0)	4	4	(100.0)	4	(100.0)	1	(25.0)
	4	4	(100.0)	4	(100.0)	4	(100.0)	5	4	(80.0)	4	(80.0)	3	(60.0)
	0	0		0		0		1	1	(100.0)	1	(100.0)	0	(0.0)
	8	8	(100.0)	8	(100.0)	4	(50.0)	8	8	(100.0)	8	(100.0)	4	(50.0)
	6	6	(100.0)	6	(100.0)	3	(50.0)	6	6	(100.0)	6	(100.0)	4	(66.7)
	24	24	(100.0)	24	(100.0)	10	(41.7)	24	24	(100.0)	24	(100.0)	10	(41.7)
	1	1	(100.0)	1	(100.0)	1	(100.0)	0	0		0		0	
	23	23	(100.0)	23	(100.0)	17	(73.9)	23	23	(100.0)	23	(100.0)	16	(69.6)
	7	7	(100.0)	7	(100.0)	5	(71.4)	7	7	(100.0)	7	(100.0)	4	(57.1)
	2	2	(100.0)	2	(100.0)	1	(50.0)	1	1	(100.0)	1	(100.0)	1	(100.0)
	7	7	(100.0)	7	(100.0)	0	(0.0)	8	7	(87.5)	7	(87.5)	0	(0.0)
	2	2	(100.0)	2	(100.0)	2	(100.0)	1	1	(100.0)	1	(100.0)	0	(0.0)
	0	0		0		0		2	2	(100.0)	2	(100.0)	1	(50.0)
	2	2	(100.0)	2	(100.0)	0	(0.0)	3	3	(100.0)	3	(100.0)	0	(0.0)
	1	1	(100.0)	1	(100.0)	0	(0.0)	0	0		0		0	
	10	10	(100.0)	10	(100.0)	4	(40.0)	13	13	(100.0)	13	(100.0)	13	(100.0)
	2	2	(100.0)	2	(100.0)	2	(100.0)	2	2	(100.0)	2	(100.0)	2	(100.0)
	4	4	(100.0)	4	(100.0)	1	(25.0)	8	8	(100.0)	8	(100.0)	3	(37.5)
Total	279	278	(99.6)	278	(99.6)	149	(53.4)	294	292	(99.3)	292	(99.3)	163	(55.4)

NOTE: Numbers shown in parentheses are percentages of the number enrolled for each investigator and treatment.

10.1.24 Discontinuations

The number of patients who discontinued from the study is summarized in Table 3 for all enrolled subjects. A subject may have had more than one reason for discontinuation, but for the

purposes of Table 3, only the primary reason was listed. Overall 57 (9.9%) of the subjects prematurely discontinued.

Clinical Reviewer's comment: Although the applicant stated the hierarchical order for discontinuation was (1) subject request, (2) treatment failure, (3) adverse event, (4) lost to follow-up, (5) admission results, and (6) other; the actual hierarchical order reflected in Table 3 is: adverse event, followed by treatment failure, followed by subject request, etc. This approach is acceptable.

Table 3 was adapted for clarity by the reviewer from Table 4 in the applicant's study report.

TABLE 3
Summary of Discontinuations

	Daytime	**Bedtime**
Enrolled	279	294
Discontinued	31 (11.1%)	26 (8.8%)
Adverse event	*3*	*7*
Treatment failure	*9*	*2*
Subject request	*2*	*1*
Admission PAP smear results (low grade sil poss HPV effect)	*0*	*1*
Lost to follow-up	*8*	*6*
*Other**	*9*	*9*

*includes non-compliance, loss of ovule, administration of medication prohibited by protocol, missed visit(s), and investigator discretion

Clinical Reviewer's Comment: The 11 subjects who discontinued due to treatment failure were all included as failures in the applicant's Intent-to-Treat analysis. In the Efficacy Evaluable population, only two of the nine subjects in the Daytime group and one of the two subjects in the Bedtime group who discontinued due to treatment failure were considered evaluable.

10.1.25 Demographics

Selected demographic and baseline characteristics by treatment group for the Efficacy Evaluable population are shown in Table 3.

TABLE 3
Demographic and Baseline Characteristics by Treatment Group
Efficacy Evaluable Population

	Daytime MONISTAT 1		Bedtime MONISTAT 1		Total		
	n	(%)	n	(%)	n	(%)	p-value
Total number of subjects (N)	149		163		312		
Age (yrs)							
N	149		163		312		
Min	16		18		16		
Max	76		71		76		
Mean	34.8		35.2		35.0		0.7369[a]
STD	12.19		13.61		12.94		
Race							
Caucasian	106	(71.1)	115	(70.6)	221	(70.8)	
Black	30	(20.1)	34	(20.9)	64	(20.5)	
Asian	1	(0.7)	2	(1.2)	3	(1.0)	
Hispanic	12	(8.1)	10	(6.1)	22	(7.1)	
Other[b]	0	(0.0)	2	(1.2)	2	(0.6)	0.7641[c]
Currently menstruating							
No	146	(98.0)	161	(98.8)	307	(98.4)	
Yes	3	(2.0)	2	(1.2)	5	(1.6)	
Pregnancy test results							
Negative	143	(96.0)	154	(94.5)	297	(95.2)	
N/A	6	(4.0)	9	(5.5)	15	(4.8)	
Intercourse between admission and return visit							
No	90	(62.9)	96	(61.1)	186	(62.0)	
Yes, did not always use condom	39	(27.3)	36	(22.9)	75	(25.0)	
Yes, always used condom	14	(9.8)	25	(15.9)	39	(13.0)	
Missing	6		6		12		
Negative clue cells							
Negative	149	(100.0)	163	(100.0)	312	(100.0)	
10% KOH yeast							
Budding yeast	31	(20.8)	30	(18.4)	61	(19.6)	
Pseudohyphae	31	(20.8)	36	(22.1)	67	(21.5)	
Budding yeast and pseudohyphae	87	(58.4)	97	(59.5)	184	(59.0)	
Disease severity group at admission[d]							
Mild (2-6)	50	(33.6)	45	(27.6)	95	(30.4)	
Moderate (7-12)	90	(60.4)	97	(59.5)	187	(59.9)	
Severe (≥13)	9	(6.0)	21	(12.9)	30	(9.6)	
Number of VVC episodes during last 12 months							
N	149		163		312		
Min	0		0		0		
Max	3		3		3		
Mean	0.7		0.6		0.6		0.1294[a]
STD	0.92		0.85		0.89		
Highest activity level							
Inactive	4	(2.7)	0		4	(2.7)	
Mild activity	39	(26.4)	0		39	(26.4)	
Moderate activity	75	(50.7)	0		75	(50.7)	
Vigorous activity	30	(20.3)	0		30	(20.3)	
Missing	1		0		1		
Other VVC products used[e]							
No	137	(93.8)	152	(93.3)	289	(93.5)	
Yes	9	(6.2)	11	(6.7)	20	(6.5)	
Missing	3		0		3		

[a] Based on t-test assuming equal variances.
[b] Other includes biracial, Mexican-Filipina.
[c] Based on Fisher's exact test.
[d] Disease severity group is the sum of sign and symptom scores at admission.
[e] Subjects who took at least one other VVC product within the first seven days per the diary.

10.1.26 Admission Vulvovaginal Signs and Symptoms

Table 4 presents a summary of the number of subjects at admission with vulvovaginal signs and symptoms by severity for the Efficacy Evaluable population. Vulvovaginal signs and symptoms were scored (as indicated in Section 10.1.4 "Inclusion Criteria" of this review) and summed to obtain a total severity score.

TABLE 4
Summary of Admission Severity of Vulvovaginal Signs and Symptoms
Efficacy Evaluable Population

Sign or Symptom	Severity	Daytime MONISTAT 1 (N=149)		Bedtime MONISTAT 1 (N=163)	
		n	(%)	n	(%)
Sign					
Erythema	Absent	3	(2.0)	8	(4.9)
	Mild	60	(40.3)	46	(28.2)
	Moderate	69	(46.3)	86	(52.8)
	Severe	17	(11.4)	23	(14.1)
Edema	Absent	50	(33.6)	41	(25.2)
	Mild	59	(39.6)	68	(41.7)
	Moderate	40	(26.8)	46	(28.2)
	Severe	0	(0.0)	8	(4.9)
Excoriation	Absent	93	(62.4)	100	(61.3)
	Mild	30	(20.1)	37	(22.7)
	Moderate	23	(15.4)	18	(11.0)
	Severe	3	(2.0)	8	(4.9)
Symptom					
Itching	Absent	6	(4.0)	8	(4.9)
	Mild	53	(35.6)	44	(27.0)
	Moderate	67	(45.0)	85	(52.1)
	Severe	23	(15.4)	26	(16.0)
Burning	Absent	32	(21.5)	37	(22.7)
	Mild	46	(30.9)	46	(28.2)
	Moderate	60	(40.3)	60	(36.8)
	Severe	11	(7.4)	20	(12.3)
Irritation	Absent	8	(5.4)	11	(6.7)
	Mild	43	(28.9)	40	(24.5)
	Moderate	76	(51.0)	79	(48.5)
	Severe	22	(14.8)	33	(20.2)

TABLE 4 continued
Summary of Admission Severity of Vulvovaginal Signs and Symptoms
Efficacy Evaluable Population

Sign or Symptom	Severity	Daytime MONISTAT 1 (N=149)		Bedtime MONISTAT 1 (N=163)	
		n	(%)	n	(%)
Total Score	**N**		**149**		**163**
	Min		**2**		**2**
	Max		**17**		**18**
	Mean		**8.0**		**8.5**
	STD		**3.05**		**3.29**

10.1.27 Summary of Fungal Species at Admission and Return Visit

A summary of fungal species present at the Admission Visit for the Intent-to-Treat and Efficacy Evaluable populations are presented in Tables 5 and 6, respectively.

TABLE 5
Summary of Admission Fungal Species:
Intent-to-Treat Population

Species	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)		Total (N=570)	
	n	(%)	n	(%)	n	(%)
Candida albicans	190	(68.3)	187	(64.0)	377	(66.1)
Candida dubliniensis	0	(0.0)	1	(0.3)	1	(0.2)
Candida glabrata	10	(3.6)	18	(6.2)	28	(4.9)
Candida krusei	3	(1.1)	2	(0.7)	5	(0.9)
Candida parapsilosis	2	(0.7)	1	(0.3)	3	(0.5)
Candida tropicalis	1	(0.4)	3	(1.0)	4	(0.7)
Missing culture	1	(0.4)	0	(0.0)	1	(0.2)
Negative culture	73	(26.3)	86	(29.5)	159	(27.9)

NOTE: Four hundred ten (410) Intent-to-Treat subjects had a positive culture at admission. A subject may have had more than one fungal species.

TABLE 6
Summary of Admission Fungal Species:
Efficacy Evaluable Population

Species	Daytime MONISTAT 1 (N=149)		Bedtime MONISTAT 1 (N=163)		Total (N=312)	
	n	(%)	n	(%)	n	(%)
Candida albicans	137	(91.9)	147	(90.2)	284	(91.0)
Candida dubliniensis	0	(0.0)	1	(0.6)	1	(0.3)
Candida glabrata	9	(6.0)	16	(9.8)	25	(8.0)
Candida krusei	2	(1.3)	2	(1.2)	4	(1.3)
Candida parapsilosis	2	(1.3)	1	(0.6)	3	(1.0)
Candida tropicalis	0	(0.0)	2	(1.2)	2	(0.6)

NOTE: Three hundred twelve (312) Efficacy Evaluable subjects had a positive culture at admission. A subject may have had more than one fungal species.

A summary of the fungal species present at the Test-of-Cure Visit for the Efficacy Evaluable population is presented in Table 7. Subjects with a positive culture at this visit were considered mycological failures.

TABLE 7
Summary of Test-of-Cure Fungal Species
Efficacy Evaluable Population

Species	Daytime MONISTAT 1 (N=149)		Bedtime MONISTAT 1 (N=163)		Total (N=312)	
	n	(%)	n	(%)	n	(%)
Candida albicans	33	(22.1)	45	(27.6)	78	(25.0)
Candida dubliniensis	0	(0.0)	1	(0.6)	1	(0.3)
Candida glabrata	7	(4.7)	9	(5.5)	16	(5.1)
Candida krusei	1	(0.7)	1	(0.6)	2	(0.6)
Candida parapsilosis	1	(0.7)	1	(0.6)	2	(0.6)
Candida tropicalis	1	(0.7)	1	(0.6)	2	(0.6)

NOTE: Ninety nine (99) Efficacy Evaluable subjects had a positive culture at the return visit. A subject may have had more than one fungal species.

Seven subjects had infections at the Test-of-Cure Visit with fungal organisms that were not present at Admission, as shown in Table 8. The presence of *Candida*, regardless of whether it was the baseline species or a new species, at the Test-of-Cure Visit, was considered a mycological failure.

Clinical Reviewer's Comment: Table 8 was created by the reviewer.

TABLE 8
***Candida* Species Isolated at Admission Compared to Test-of-Cure Visit**

Treatment Group	Subject #	*Candida* species Isolated	
		Admission Culture	**Test-of-Cure Culture**
Daytime	69606	*C. albicans*	*C. glabrata*
	63406	*C. albicans*	*C. lusitaniae*
	52509	*C. glabrata*	*C. glabrata* and *C. tropicalis*
	68607	*C. glabrata*	*C. albicans*
	61506	*C. krusei*	*C. parapsilosis*
Bedtime	57107	*C. albicans*	*C. glabrata*
	55707	*C. albicans*	*C. albicans* (interim visit) *C. parapsilosis* (TOC visit)

The clinical and mycological outcomes of subjects stratified by baseline pathogen are shown in Table 1 in Section 6.1.5 (Clinical Microbiology) of this review. For *C. albicans*, the most common species isolated, the percentage of patients with resolution of VVC symptoms and eradication of their baseline pathogen was similar in the two treatment groups (62% [84/135] in the Daytime group and 55% [79/143] in the Bedtime group).

Susceptibility testing of isolates collected at admission and Test-of-Cure was performed using the NCCLS microbroth dilution method (M27A). Breakpoints for miconazole have not been established. The baseline miconazole MIC values of *C. albicans* and *C. glabrata* isolates from patients who showed resolution of VVC symptoms and those who failed clinically overlapped (Table 3 in Section 6.1.5). The number of patients with *Candida* species other than *C. albicans* (*C. krusei, C. parapsilosis,* and *C. tropicalis*) were too small to correlate the baseline miconazole MIC values with clinical outcome. Although changes (increase or decrease) in MIC were noted in pre-treatment and post-treatment isolates, these changes did not correlate with clinical outcome.

When baseline miconazole MIC values were compared with baseline MIC values for fluconazole, clotrimazole, terconazole, and butoconazole (Table 4 in Section 6.1.5), the results showed that some isolates with high miconazole MIC values (16-32 µg/ml) also showed increase in MIC values for azoles other than miconazole (clotrimazole, terconazole, fluconazole, and/or butoconazole), suggesting cross-resistance between azoles.

10.1.28 Compliance

To be considered compliant, a subject had to use the ovule within 48 hours of the Admission Visit; a subject also had to remain in bed for at least 30 minutes after ovule insertion if randomized to the Bedtime group, or insert the ovule within six hours after arising if randomized to the Daytime group.

Compliance results are shown in Table 9. Only 3 subjects were considered non-compliant (one in the Daytime group and two in the Bedtime group). All 3 subjects complied with dosage administration, but had their ovule dislodged after insertion according to the CRF:

Daytime group

- 64509: subject noted the ovule fell out 2 hours after insertion; investigator thought it sounded like the outer shell may have fallen out and not the entire ovule

Bedtime group

- 55808: subject found the ovule in bed as she was making it the following morning
- 58787: ovule fell out while the subject was sleeping

All three subjects were excluded from the Efficacy Evaluable population for other reasons.

Clinical reviewer's Comment: An additional subject in the Bedtime group (63707) was noted in the CRF to have the ovule fall into the toilet as she was trying to insert it. The subject used the external cream alone. The primary reason for exclusion of this subject by the applicant from the Efficacy Evaluable population was "study drug used incorrectly."

TABLE 9
Compliance in the Safety Population

	Daytime	**Bedtime**
Compliant*	277/278 (99.6)	290/292 (99.3)

* to be compliant a patient must have used the ovule with or without the external cream and the ovule must not have fallen out

Use of the external vaginal cream in addition to the ovule in the safety population is shown in Table 10. The external vaginal cream was used in addition to the ovule by 61.9% (353/570) of the subjects overall. No information was recorded on whether or not 5.6% (32/570) subjects used the cream.

Clinical Reviewer's Comment: Table 10 was created by the Reviewer.

TABLE 10
Use of the External Cream in the Safety Population

	Daytime N=278	**Bedtime N=292**
Ovule Plus External Cream	180 (64.7%)	173 (59.2%)
Ovule Alone	81 (29.1%)	104 (35.6%)
Missing Data	17 (6.1%)	15 (5.1%)

10.1.29 Efficacy Results

Therapeutic, Mycological, and Clinical Cure Rates
A summary of the therapeutic, mycological, and clinical cure rates at the Test-of-Cure Visit for the Intent-to-Treat and Efficacy Evaluable populations are shown in Tables 11 and 12, respectively. The therapeutic cure rate was derived from the clinical and mycological responses at the Test-of-Cure Visit and was defined as both a mycological and clinical cure.

In the Efficacy Evaluable population, the lower bound of the 95% confidence interval for the treatment difference (Daytime minus Bedtime) in the therapeutic cure rates lies above -15%, indicating that the efficacy of daytime and bedtime administration are non-inferior, according to the primary endpoint of the study. In addition, the lower bound of the confidence interval for the therapeutic cure rates in the Intent-to-Treat population and both the mycological and clinical cure rates in both populations, also lie above -15%.

Clinical Reviewer's Comment: Tables 11 and 12 were adapted for clarity from Tables 8.1 and 8.2 in the applicant's study report.

TABLE 11
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
Intent-to-Treat Population

	Daytime	Bedtime
Therapeutic Cure	**121/278 (43.5)**	**103/292 (35.3)**
	95% CI [0.1, 16.4]	
Mycological Cure	141/278 (50.7)*	130/292 (44.5)*
	95% CI [-2.2, 14.6]	
Clinical Cure	195/278 (70.1)**	196/292 (67.1)**
	95% CI [-4.8, 10.8]	

* p = 0.1539 by Fisher's exact test
** p = 0.4705 by Fisher's exact test

TABLE 12
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
Efficacy Evaluable Population

	Daytime	Bedtime
Therapeutic Cure	**86/149 (57.5)**	**83/163 (50.9)**
	95% CI [-4.6, 18.2]	
Mycological Cure	105/149 (70.5)*	104/163 (63.8)*
	95% CI [-4.1, 17.4]	
Clinical Cure	111/149 (74.5)**	120/163 (73.6)**
	95% CI [-9.2, 10.9]	

* p = 0.2294 by Fisher's exact test
** p = 0.8976 by Fisher's exact test

Clinical Reviewer's Comments: Patients were also analyzed by the Statistical and Clinical Reviewers according to randomization code, and not according to how they actually used the study drug. The resulting therapeutic, mycological, and clinical cure rates for the Intent-to-Treat and Efficacy Evaluable populations are shown below in Tables 13 and 14, respectively. These results are not substantially different from the results as determined by the applicant. The tables were created by the Reviewer.

TABLE 13
***FDA Analysis* - Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit According to Randomization and Not Actual Use**
Intent-to-Treat Population

	Daytime N=284	**Bedtime N=286**
Therapeutic Cure	**119 (41.9%)**	**105 (36.7)**
	95% CI [-3.0, 13.4]	
Mycological Cure	142 (50.0%)	129 (45.1%)
Clinical Cure	193 (67.9%)	198 (69.2%)

TABLE 14
***FDA Analysis* - Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit According to Randomization and Not Actual Use**
Efficacy Evaluable Population

	Daytime N=155	**Bedtime N=157**
Therapeutic Cure	**86 (55.5%)**	**83 (52.9%)**
	95% CI [-8.8, 14.0]	
Mycological Cure	108 (69.7%)	101 (64.3%)
Clinical Cure	111 (71.6%)	120 (76.4%)

Clinical Reviewer's Comment: The Statistical and Clinical Reviewers analyzed the cure rates for the subset of subjects by treatment group who used the external cream in addition to the ovule compared to those subjects who used only the ovule. The cure rates, as shown in Tables 15 and 16 for the Intent-to-Treat and Efficacy Evaluable populations, respectively, are similar in both the Daytime and Bedtime groups whether or not the subjects used the cream in addition to the ovule. The use of the ovule alone in both populations was associated with the lowest reported therapeutic cure rates. Tables 15 and 16 were created by the Reviewers.

TABLE 15
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
Ovule Plus External Cream Compared to Ovule Use Alone
Intent-to-Treat Population

	Daytime (N=278)*		Bedtime (N=292)**	
	Ovule Plus Cream N=180	**Ovule Alone N=81**	**Ovule Plus Cream N=173**	**Ovule Alone N=104**
Therapeutic Cure	**74 (41.1%)**	**40 (49.4%)**	**64 (37.0%)**	**33 (31.7%)**
Mycological Cure	86 (47.8%)	45 (55.5%)	78 (45.1%)	45 (43.3%)
Clinical Cure	125 (69.4%)	57 (70.4%)	120 (69.4%)	66 (63.5%)

* Seventeen (17) subjects in the Daytime group did not have information recorded on whether or not they used the external cream
** Fifteen (15) subjects in the Daytime group did not have information recorded on whether or not they used the external cream

TABLE 16
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
Ovule Plus External Cream Compared to Ovule Use Alone
Efficacy Evaluable Population

	Daytime (N=149)*		Bedtime (N=163)**	
	Ovule Plus Cream N=96	**Ovule alone N=40**	**Ovule Plus Cream N=97**	**Ovule alone N=56**
Therapeutic Cure	**54 (56.2%)**	**25 (62.5%)**	**54 (55.7%)**	**23 (41.1%)**
Mycological Cure	65 (67.8%)	30 (75.0%)	65 (67.0%)	32 (57.1%)
Clinical Cure	72 (75.0%)	30 (75.0%)	75 (77.3%)	37 (66.1%)

* Thirteen (13) subjects in the Daytime group did not have information recorded on whether or not they used the external cream
** Ten (10) subjects in the Daytime group did not have information recorded on whether or not they used the external cream

Clinical Reviewer's Comment: Although not specified by the applicant, the Statistical and Clinical Reviewer's evaluated efficacy results in a Modified Intent-to-Treat population, as shown in Table 17, consisting of subjects who used study drug (ovule with orwithout the external vulvar cream) and had a positive culture at the Admission Visit for Candida. Subjects who discontinued and those with missing outcome data were considered to be treatment failures. Table 17 was created by the Reviewers.

TABLE 17
***FDA Analysis* - Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit**
Modified-Intent-to-Treat Population

	Daytime N=204	**Bedtime N=206**
Therapeutic Cure	**121 (59.3%)**	**103 (50.0%)**
	95% CI [-0.5, 19.2]	
Mycological Cure	141 (69.1%)	130 (63.1%)
	95% CI [-3.4, 15.4]	
Clinical Cure	151 (74.0%)	147 (71.4%)
	95% CI [-6.2, 11.5]	

Correlation between Clinical and Mycological Cure

The correlation between clinical and mycological cure rates in the Efficacy Evaluable population for the Daytime and Bedtime groups are shown in Tables 18 and 19, respectively. The Kappa Statistic, which can range from -1 to 1, is a quantitative measure of reproducibility of drug benefit measured with two nominal endpoints. A Kappa value of 1 means perfect positive correlation, while a Kappa of -1 means perfect negative correlation. In this study, the Kappa is used to evaluate the correlation between clinical and microbiological response. Both values of Kappa, for daytime and bedtime administration, show positive values. Therefore, it can be said that clinical and mycological cure rates were weakly, but positively correlated.

Clinical Reviewer's Comment: Table 18 and Table 19 were created by the reviewer using data from Table 9 in the applicant's study report. The Kappa statistic variable was calculated by the Statistical Reviewer and added as a footnote to both tables.

TABLE 18
Correlation of Clinical and Mycological Cure Rates for the Daytime Group
Efficacy Evaluable Population*

Clinical Response	**Mycological Response**		
	Cure	**Failure**	**Missing/Not Interpretable**
Cure	86 (57.7)	25 (16.8)	0
Failure	19 (12.8)	16 (10.7)	1 (0.7)
Non-Evaluable	0	0	2 (1.3)

* Kappa = 0.219

TABLE 19
Correlation of Clinical and Mycological Cure Rates for the Bedtime Group
Efficacy Evaluable Population*

Clinical Response	Mycological Response		
	Cure	Failure	Missing/Not Interpretable
Cure	83 (50.9)	37 (22.7)	0
Failure	21 (12.9)	20 (12.3)	0
Non-Evaluable	0	0	2 (1.2)

* Kappa = 0.159

Cure Rates by Activity Level

The therapeutic, mycological, and clinical cure rates at the Test-of-Cure Visit in the Intent-to-Treat and Efficacy Evaluable populations presented by activity level in the Daytime group are shown in Tables 20 and 21, respectively.

TABLE 20
Cure Rates in the Daytime Group by Activity Level
Intent-to-Treat Population

Response/Group	Low Activity Level		High Activity Level		Fisher's Exact Test
	n/N	(%)	n/N	(%)	
Therapeutic Cure Rates[a]	39/80	(48.8)	80/186	(43.0)	0.4212
Mycological Cure Rates	48/80	(60.0)	91/186	(48.9)	0.1091
Clinical Cure Rates	53/80	(66.3)	140/186	(75.3)	0.1368

[a] Therapeutic cure is defined when both mycological and clinical responses are considered cured at the Test-of-Cure Visit

NOTE: A subject was classified into the high activity level if the activity assessment was either moderate or vigorous (186, 69.9%) at any one of the four hourly evaluations: otherwise the subject was classified into the low activity level

TABLE 21
Cure Rates in the Daytime Group by Activity Level
Efficacy Evaluable Population

Response/Group	Low Activity Level		High Activity Level		Fisher's Exact Test
	n/N	(%)	n/N	(%)	
Therapeutic cure rates[a]	26/43	(60.5)	59/105	(56.2)	0.7154
Mycological cure rates	35/43	(81.4)	69/105	(65.7)	0.0746
Clinical cure rates	30/43	(69.8)	80/105	(76.2)	0.4156

[a] Therapeutic cure is defined when both mycological and clinical responses are considered cured at the Test-of-Cure Visit.
NOTE: A subject was classified into the high activity level if the activity assessment was either moderate or vigorous (105, 70.9%) at any one of the four hourly evaluations; otherwise the subject was classified into the low activity level.

Clinical Reviewer's Comment: The applicant specified that they would analyze the efficacy for subjects in the Daytime group based upon classification into two activity levels – low and high. The Statistical and Clinical Reviewers also compared subjects by all of the four activity levels specified in the protocol for the Daytime group (inactive, mild, moderate, and vigorous). The results in the Intent-to-Treat and Efficacy Evaluable populations are shown in Tables 22 and 23, respectively. Tables 22 and 23 were created by the Reviewers.

TABLE 22
***FDA Analysis* - Therapeutic, Mycological, and Clinical Cure Rates by All Activity Levels**
Intent-to-Treat Population

Response	Inactive		Mild Activity		Moderate Activity		Vigorous Activity	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Therapeutic cure rates	5/7	(71.4)	34/73	(46.6)	51/135	(37.8)	97/135	(71.9)
Mycological cure rates	5/7	(71.4)	43/73	(58.9)	62/135	(45.9)	29/51	(56.9)
Clinical cure rates	5/7	(71.4)	48/73	(65.8)	97/135	(71.9)	43/51	(84.3)

TABLE 23
***FDA Analysis* - Therapeutic, Mycological, and Cure Rates by All Activity Levels**
Efficacy Evaluable Population

Response	Inactive		Mild Activity		Moderate Activity		Vigorous Activity	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Therapeutic cure rates	4/4	(100)	22/39	(56.4)	38/75	(50.7)	21/30	(70.0)
Mycological cure rates	4/4	(100)	31/39	(79.5)	48/75	(64.0)	21/30	(70.0)
Clinical cure rates	4/4	(100)	26/39	(66.7)	54/75	(72.0)	26/30	(86.7)

Cure Rates by Age and Race

Cure rates in the Intent-to-Treat and Efficacy Evaluable populations were compared for subjects less than 65 years of age to those who were 65 years of age and older, as shown in Tables 23 and 24. Conclusions about differences in cure rates between the younger and older subjects are not meaningful due to the small number of older subjects.

Clinical Reviewer's Comment: Tables 23 and 24 were created by the reviewer.

TABLE 23
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
By Age (16 to 64 years and ≥ 65 years)
Intent-to-Treat Population

	Daytime (N=278)		Bedtime (N=292)	
	16-64 years N=272	≥ 65 years N=6	18-64 years N=282	≥ 65 years N=10
Therapeutic Cure	**119 (43.7%)**	**2 (33.3%)**	**102 (36.2%)**	**1 (10.0%)**
Mycological Cure	138 (50.7%)	3 (50.0%)	128 (45.5%)	2 (20.0%)
Clinical Cure	192 (70.6%)	3 (50.0%)	194 (68.8%)	2 (20.0%)

TABLE 24
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
By Age (< 65 years and ≥ 65 years)
Efficacy Evaluable Population

	Daytime (N=149)		Bedtime (N=163)	
	16-64 years N=146	≥ 65 years N=3	18-64 years N=158	≥ 65 years N=5
Therapeutic Cure	**84 (57.5%)**	**2 (66.7%)**	**82 (51.9%)**	**1 (20.0%)**
Mycological Cure	102 (69.7%)	3 (100%)	102 (64.5%)	2 (40.0%)
Clinical Cure	109 (74.7%)	2 (66.7%)	118 (74.7%)	2 (40.0%)

Cure rates in the Intent-to-Treat and Efficacy Evaluable populations were compared for female subjects by race (Caucasian, Black and Hispanic), as shown in Tables 25 and 26. In the Reviewer's opinion, any differences seen in cure rates between Caucasian, Black, and Hispanic subjects are not considered clinically meaningful and no changes to the recommended dosing of Monistat 1 Combination Pack are warranted based on race.

Clinical Reviewer's Comment: Tables 25 and 26 were created by the reviewer.

TABLE 25
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
By Race (Caucasian, Black and Hispanic)
Intent-to-Treat Population

	Daytime (N=276)*			Bedtime (N=285)**		
	Caucasian N=189	**Black N=61**	**Hispanic N=26**	**Caucasian N=197**	**Black N=60**	**Hispanic N=28**
Therapeutic Cure	**84 (44.4%)**	**28 (45.9%)**	**9 (34.6%)**	**72 (36.5%)**	**16 (26.7%)**	**13 (46.4%)**
Mycological Cure	101 (53.7%)	29 (47.5%)	11 (42.3%)	92 (46.7%)	21 (35%)	14 (50.0%)
Clinical Cure	131 (69.3%)	44 (72.1%)	20 (76.9%)	131 (66.5%)	42 (70.0%)	18 (64.3%)

* two subjects (Asian) were not included
**7 subjects (5 Asian and 2 "other") were not included

TABLE 26
Therapeutic, Mycological, and Clinical Cure Rates at Test-of-Cure Visit
By Race (Caucasian, Black and Hispanic)
Efficacy Evaluable Population

	Daytime (N=148)*			Bedtime (N=159)**		
	Caucasian N=106	**Black N=30**	**Hispanic N=12**	**Caucasian N=115**	**Black N=34**	**Hispanic N=10**
Therapeutic Cure	**60 (56.6%)**	**21 (70.0%)**	**5 (41.7%)**	**60 (52.2%)**	**14 (41.2%)**	**8 (80.0%)**
Mycological Cure	76 (71.7%)	22 (73.3%)	7 (58.3%)	76 (66.1%)	18 (52.9%)	8 (80.0%)
Clinical Cure	76 (71.7%)	26 (86.7%)	9 (75.0%)	83 (72.2%)	25 (73.5%)	10 (100%)

* one subject (Asian) was not included
**4 subjects (2 Asian and 2 "other") were not included

Use of Additional Antifungal Treatment
Additional antifungal treatment was prescribed at the Interim or Test-of-Cure Visit for 43 subjects in the Daytime group and 44 subjects in the Bedtime group (Intent-to-Treat population). The specific drugs used by subjects in the Daytime and Bedtime groups are shown below.

In the Daytime group the following antifungals were administered: fluconazole (N=22), fluconazole plus terconazole (N=2), fluconazole plus miconazole (N=1), butoconazole (N=1), Lotrisone® (N=1), Lotrisone® plus terconazole (N=1); miconazole (N=3); Mycolog® (N=2); Mytrex® (N=1); and terconazole (N=10).

In the Bedtime group the following antifungals were administered: fluconazole (N=16); fluconazole plus Mycolog® (N=1); miconazole (N=3); miconazole plus fluconazole (N=1); Mycolog® (N=1); terconazole (N=9); Lostrisone® (N=1); and Mycolog® (N=1).

Clinical Reviewer's Comment: All subjects were considered therapeutic failures by the applicant, as appropriate, with the exception of one subject in the Daytime group (6807) who

received one dose of fluconazole and was considered a therapeutic cure. The applicant's analysis will not be recalculated in order to reassign one subject.

Estimated Time to Initial Relief of Vulvovaginal Symptoms
The estimated time to initial relief of the individual vulvovaginal symptoms of itching, burning, irritation, and all 3 symptoms combined were analyzed for the Efficacy Evaluable population by treatment group. The results are summarized below (detailed results not shown):

- Itching: median time to relief was 36 hours for both groups; p = NS
- Burning: median time to relief was 24 hours in the Daytime group and 36 hours in the Bedtime group; p = NS
- Irritation: median time to relief was 48 hours in the Daytime group and 42 hours in the Bedtime group; p = NS
- All 3 symptoms combined: median time to relief was 72 hours for both groups; p = NS

Comparisons between treatment schedules for the Intent-to-Treat population also showed no statistically significant difference between the Daytime and Bedtime groups for the estimated time to relief of itching, burning, and irritation, and for all three symptoms combined (data not shown).

10.1.30 Safety Results

In the safety population there were 143 (51.4%) subjects in the Daytime group, and 140 (47.9%) subjects in the Bedtime group who reported at least one treatment-emergent adverse event during the study, as shown in Table 27. Subjects with multiple adverse events in one body system were only counted once in that system. Table 28 lists the incidence of specific adverse events within each body system.

TABLE 27
Adverse Events by Body System
Safety Population

Body system	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Total subjects reporting adverse events	143	(51.4)	140	(47.9)
Ear and labyrinth disorders	0	(0.0)	3	(1.0)
Eye disorders	1	(0.4)	0	(0.0)
Gastrointestinal disorders	21	(7.6)	28	(9.6)
General disorders and administration site conditions	10	(3.6)	3	(1.0)
Immune system disorders	1	(0.4)	2	(0.7)
Infections and infestations	31	(11.2)	35	(12.0)
Injury, poisoning and procedural complications	6	(2.2)	0	(0.0)
Metabolism and nutrition disorders	2	(0.7)	1	(0.3)
Musculoskeletal and connective tissue disorders	10	(3.6)	23	(7.9)
Nervous system disorders	40	(14.4)	39	(13.4)
Psychiatric disorders	7	(2.5)	11	(3.8)
Renal and urinary disorders	1	(0.4)	5	(1.7)
Reproductive system and breast disorders	74	(26.6)	77	(26.4)
Respiratory, thoracic and mediastinal disorders	14	(5.0)	12	(4.1)
Skin and subcutaneous tissue disorders	8	(2.9)	6	(2.1)
Vascular disorders	2	(0.7)	0	(0.0)

NOTE: Percentages are the proportions of subjects within that category.

TABLE 28
Incidence and Total Number of Subjects Reporting Adverse Events Summarized by Body System and Preferred Term
Safety Population

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Total Subjects Reporting Adverse Events	143	(51.4)	140	(47.9)
Reproductive System and Breast Disorders	74	(26.6)	77	(26.4)
Vulvovaginal Discomfort	52	(18.7)	63	(21.6)
Dysmenorrhea	9	(3.2)	10	(3.4)
Genital Pruritus Female	6	(2.2)	4	(1.4)
Vaginal Irritation	4	(1.4)	2	(0.7)
Vaginal Discharge	3	(1.1)	1	(0.3)
Metrorrhagia	2	(0.7)	2	(0.7)
Pelvic Pain NOS	2	(0.7)	2	(0.7)
Vulvovaginal Disorder NOS	2	(0.7)	2	(0.7)
Menses Delayed	1	(0.4)	1	(0.3)
Ovarian Cyst	1	(0.4)	0	(0)
Vulval Laceration	1	(0.4)	0	(0)
Menstruation Irregular	0	(0)	1	(0.3)
Premenstrual Syndrome	0	(0)	1	(0.3)
Vaginal Hemorrhage	0	(0)	3	(1.0)
Nervous System Disorders	40	(14.4)	39	(13.4)
Headache	40	(14.4)	34	(11.6)
Sinus Headache	1	(0.4)	3	(1.0)
Somnolence	1	(0.4)	0	
Dizziness	0		2	(0.7)
Dysgeusia	0		1	(0.3)
Migraine NOS	0		2	(0.7)
Infections and Infestations	31	(11.2)	35	(12.0)
Fungal Infection NOS	5	(1.8)	2	(0.7)
Sinusitis NOS	5	(1.8)	5	(1.7)
Vaginitis Bacterial NOS	5	(1.8)	4	(1.4)
Vaginosis Fungal NOS	3	(1.1)	0	(0)
Herpes Simplex	2	(0.7)	1	(0.3)
Nasopharyngitis	2	(0.7)	5	(1.7)
Urinary Tract Infection NOS	2	(0.7)	3	(1.0)
Bladder Infection NOS	1	(0.4)	0	
Herpes Zoster	1	(0.4)	1	(0.3)

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Pharyngitis	1	(0.4)	0	
Pharyngitis Streptococcal	1	(0.4)	0	
Sinusitis Acute NOS	1	(0.4)	0	
Vulvovaginitis NOS	1	(0.4)	1	(0.3)
Candidal Infection NOS	1	(0.4)	0	
Bronchial Infection	1	(0.4)	0	
Breast Infection NOS	0		1	(0.3)
Cellulitis	0		2	(0.7)
Ear Infection NOS	0		1	(0.3)
Folliculitis	0		1	(0.3)
Pyelonephritis NOS	0		1	(0.3)
Skin Fungal Infection NOS	0		1	(0.3)
Tooth Abscess	0		1	(0.3)
Upper Respiratory Tract Infection NOS	0		6	(2.1)
Vaginitis	0		1	(0.3)
Oral Infection	0		1	(0.3)
Otitis Externa NOS	0		1	(0.3)
Ear Infection Staphylococcal	0		1	(0.3)
Gastrointestinal Disorders	21	(7.6)	28	(9.6)
Diarrhea NOS	6	(2.2)	5	(1.7)
Abdominal Pain NOS	3	(1.1)	5	(1.7)
Constipation	3	(1.1)	0	
Dyspepsia	3	(1.1)	3	(1.0)
Toothache	3	(1.1)	2	(0.7)
Abdominal Discomfort	2	(0.7)	1	(0.3)
Abdominal Distension	2	(0.7)	0	
Nausea	2	(0.7)	7	(2.4)
Abdominal Pain Upper	1	(0.4)	2	(0.7)
Loose Stools	1	(0.4)	0	
Vomiting NOS	1	(0.4)	2	(0.7)
Dental Discomfort	1	(0.4)	0	
Abdominal Pain Lower	0		2	(0.7)
Flatulence	0		1	(0.3)
Gastroesophageal Reflux Disease	0		3	(1.0)
Gastrointestinal Upset	0		1	(0.3)
Hemorrhoids	0		1	(0.3)
Oral Pain	0		1	(0.3)
Pruritus Ani	0		1	(0.3)

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Respiratory, Thoracic and Mediastinal Disorders	14	(5.0)	12	(4.1)
Cough	5	(1.8)	1	(0.3)
Pharyngolaryngeal Pain	3	(1.1)	6	(2.1)
Upper Respiratory Tract Congestion	3	(1.1)	0	
Asthma NOS	1	(0.4)	0	
Bronchitis NOS	1	(0.4)	2	(0.7)
Nasal Congestion	1	(0.4)	4	(1.4)
Nasal Passage Irritation	1	(0.4)	0	
Rhinorrhoea	1	(0.4)	1	(0.3)
Postnasal Drip	0		1	(0.3)
Rhinitis NOS	0		1	(0.3)
Sinus Pain	0		1	(0.3)
Sneezing	0		1	(0.3)
General Disorders and Administration Site Conditions	10	(3.6)	3	(1.0)
Pyrexia	3	(1.1)	1	(0.3)
Fatigue	2	(0.7)	1	(0.3)
Edema NOS	2	(0.7)	0	
Application Site Pain	1	(0.4)	0	
Influenza Like Illness	1	(0.4)	0	
Edema Peripheral	1	(0.4)	0	
Pain NOS	1	(0.4)	0	
Hangover	0		1	(0.3)
Musculoskeletal and Connective Tissue Disorders	10	(3.6)	23	(7.9)
Back Pain	4	(1.4)	10	(3.4)
Pain in Extremity	2	(0.7)	1	(0.3)
Arthralgia	1	(0.4)	4	(1.4)
Muscle Cramp	1	(0.4)	2	(0.7)
Neck Pain	1	(0.4)	3	(1.0)
Pain in Jaw	1	(0.4)	0	
Musculoskeletal Discomfort	1	(0.4)	0	
Chest Wall Pain	0		1	(0.3)
Myalgia	0		4	(1.4)
Tendonitis	0		1	(0.3)
Skin and Subcutaneous Tissue Disorders	8	(2.9)	6	(2.1)
Erythema	4	(1.4)	3	(1.0)
Dermatitis Contact	1	(0.4)	0	

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Rash NOS	1	(0.4)	2	(0.7)
Rash Pruritic	1	(0.4)	0	
Sweating Increased	1	(0.4)	0	
Urticaria NOS	0		1	(0.3)
Psychiatric Disorders	7	(2.5)	11	(3.8)
Insomnia	4	(1.4)	8	(2.7)
Depression	2	(0.7)	0	
Abnormal Dreams	1	(0.4)	0	
Sleep Disorder NOS	0		2	(0.7)
Schizophrenia, Undifferentiated Type	0		1	(0.3)
Injury, Poisoning and Procedural Complications	6	(2.2)	0	
Excoriation	4	(1.4)	0	
Joint Sprain	1	(0.4)	0	
Limb Injury NOS	1	(0.4)	0	
Metabolism and Nutrition Disorders	2	(0.7)	1	(0.3)
Diabetes Mellitus NOS	1	(0.4)	0	
Hypercholesterolemia	1	(0.4)	0	
Hypertriglyceridemia	1	(0.4)	0	
Anorexia	0		1	(0.3)
Vascular Disorders	2	(0.7)	0	
Flushing	1	(0.4)	0	
Hypertension NOS	1	(0.4)	0	
Eye Disorders	1	(0.4)	0	
Eye Pruritus	1	(0.4)	0	
Immune System Disorders	1	(0.4)	2	(0.7)
Hypersensitivity NOS	1	(0.4)	1	(0.3)
Seasonal Allergy	0		1	(0.3)
Renal and Urinary Disorders	1	(0.4)	5	(1.7)
Dysuria	1	(0.4)	2	(0.7)
Cystitis NOS	0		1	(0.3)
Hypertonic Bladder	0		1	(0.3)
Micturition Urgency	0		1	(0.3)
Ear and Labyrinth Disorders	0		3	(1.0)
Ear Pain	0		1	(0.3)
Motion Sickness	0		1	(0.3)
Sensation of Block in Ear	0		1	(0.3)

NOTE: Percentages are the proportions of subjects within that category

Severity

Most events were mild or moderate in severity. A total of 33 (11.9%) adverse events in the Daytime group and 37 (12.7%) adverse events in the Bedtime group were considered to be severe by the investigator, as shown in Table 29. The most common severe adverse event in both groups was vulvovaginal discomfort (6.1% and 6.2%, respectively).

Clinical Reviewer's Comment: Table 29 was created by the reviewer using data from Table 20 in the applicant's study report.

TABLE 29
Severe Adverse Events
Safety Population

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Total Subjects Reporting Severe Adverse Events	33	(11.9)	37	(12.7)
Reproductive system and breast disorders	18	(6.5)	18	(6.2)
Vulvovaginal discomfort	17	(6.1)	18	(6.2)
Dysmenorrhea	1	(0.4)	0	(0)
Vulvovaginal disorder NOS	1	(0.4)	0	(0)
Premenstrual syndrome	0	(0)	1	(0.3)
Vaginal hemorrhage	0	(0)	1	(0.3)
Nervous system disorders	8	(2.9)	6	(2.1)
Headache	8	(2.9)	5	(1.7)
Somnolence	1	(0.4)	0	(0)
Migrane NOS	0	(0)	1	(0.3)
Infections and infestations	2	(0.7)	7	(2.4)
Fungal infection NOS	1	(0.4)	0	(0)
Sinusitis	1	(0.4)	1	(0.3)
Vaginitis bacterial NOS	1	(0.4)	1	(0.3)
Herpes simplex	0	(0)	1	(0.3)
Herpes zoster	0	(0)	1	(0.3)
Tooth abscess	0	(0)	1	(0.3)
Upper respiratory tract infection NOS	0	(0)	1	(0.3)
Ear infection staphylococcal	0	(0)	1	(0.3)
Gastrointestinal disorders	5	(1.8)	4	(1.4)
Diarrhea NOS	2	(0.7)	0	(0)
Abdominal pain NOS	1	(0.4)	0	(0)
Abdominal discomfort	1	(0.4)	0	(0)
Abdominal pain upper	0	(0)	1	(0.3)

Body System/Primary Term	Daytime MONISTAT 1 (N=278)		Bedtime MONISTAT 1 (N=292)	
	n	(%)	n	(%)
Vomiting NOS	1	(0.4)	0	(0)
Dental discomfort	1	(0.4)	0	(0)
Abdominal pain lower	0	(0)	1	(0.3)
Gastroesophageal reflux disease	0	(0)	1	(0.3)
Oral pain	0	(0)	1	(0.3)
Respiratory, thoracic and mediastinal disorders	0	(0)	4	(0.4)
Pharyngolaryngeal pain	0	(0)	2	(0.7)
Bronchitis NOS	0	(0)	1	(0.3)
Rhinorrhea	0	(0)	1	(0.3)
Sneezing	0	(0)	1	(0.3)
General disorders and administration site conditions	3	(1.1)	1	(0.3)
Fatigue	2	(0.7)	1	(0.3)
Application site pain	1	(0.4)	0	(0)
Musculoskeletal and connective tissue disorders	0	(0)	3	(1.0)
Back pain	0	(0)	2	(0.7)
Neck pain	0	(0)	1	(0.3)
Skin and subcutaneous tissue disorders	2	(0.7)	0	(0)
Rash pruritic	1	(0.4)	0	(0)
Sweating increased	1	(0.4)	0	(0)
Psychiatric disorders	1	(0.4)	1	(0.3)
Abnormal dreams	1	(0.4)	0	(0)
Schizophrenia, undifferentiated type	0	(0)	1	(0.3)
Injury, poisoning, and procedural complications	1	(0.4)	1	(0.3)
Excoriation	1	(0.4)	0	(0)
Immune system disorders	1	(0.4)	1	(0.3)
Hypersensitivity NOS	1	(0.4)	1	(0.3)
Renal and urinary disorders	1	(0.4)	2	(0.7)
Dysuria	0	(0)	1	(0.3)
Micturition urgency	0	(0)	1	(0.3)
Ear and labyrinth disorders	0	(0)	1	(0.3)
Ear pain	0	(0)	1	(0.3)

NOTE: Percentages are the proportions of subjects within that category

Relationship to Study Drug
In the Daytime group, eight (2.9%) adverse events were considered to be of highly probable relationship to study drug by the investigator; four (1.4%) adverse events were considered of probable relationship, and 22 (7.9%) adverse events were considered of possible relationship. In the Bedtime group, six (2.1%) adverse events were considered to be of highly probable relationship to study drug by the investigator; seven (2.4%) adverse events were considered of probable relationship, and 32 (11.0%) adverse events were considered of possible relationship. In both groups, the majority of adverse events with highly probable, probable, or possible relationship to study drug were vulvovaginal discomfort.

Deaths
No deaths were reported during the study.

Serious Adverse Events
There were three serious adverse events reported by two subjects in the Bedtime group during the study. Subject 58009 (Bedtime group) experienced undifferentiated schizophrenia, and Subject 63907 (Daytime group) experienced nausea and vomiting NOS. All events were considered not related or of unlikely relationship to study drug. Narrative descriptions of these subjects appear below; day of adverse event onset is in reference to the number of days after start of study drug.

Subject 58009 (Undifferentiated Schizophrenia)
A 31-year-old Caucasian female had a medical history that included seasonal allergies, osteopenia, undifferentiated schizophrenia, obsessive-compulsive disorder, anxiety, and major depression. The subject was randomly assigned to the Bedtime group. On Day 20, the subject experienced (worsening) undifferentiated schizophrenia that required hospitalization. The event was considered by the investigator to be of severe intensity and not related to study drug. The event resolved on Day 26, and the subject completed the study. Concomitant medications at the time of the event included Luvox (fluvoxamine maleate), BuSpar (buspirone), Remeron (mirtazapine), Abilify (aripiprazole), and Pepto-Bismol (bismuth salicylate).

Subject 63907 (Nausea; Vomiting NOS)
A 34-year-old Caucasian female had a medical history that included gastroenteritis, urinary tract infection, tubal ligation, and alcoholism or drug abuse within the past two years. The subject was randomly assigned to the Daytime group. On Day 3, the subject was hospitalized for nausea and vomiting NOS. That same day, the subject also experienced dyspepsia and had a urinary tract infection NOS, both of moderate severity and of unlikely relationship to study drug. During hospitalization, a urine toxicology screen revealed current use of cocaine and cannabinoid. The events of nausea and vomiting NOS were considered by the investigator to be of moderate and severe intensity, respectively; both events were of unlikely relationship to study drug. The nausea and urinary tract infection resolved on Day 6, and the subject was discharged the following day with resolved vomiting and a diagnosis of gastroenteritis. The dyspepsia resolved on Day 25, and the subject completed the study. Concomitant medications at the time of the event included Prilosec (omeprazole), Phenergan (promethazine), IV fluid, Bactrim DS (co-trimoxazole), and Protonix (pantoprazole).

Clinical Reviewer's Comment: The Reviewer agrees with the Investigator's assessment in both cases.

Discontinuations Due to Adverse Events

Tables 30 and 31 presents a listing of subjects in the safety evaluable population evaluable that discontinued from the study due to adverse events for the Daytime and Bedtime groups, respectively. Of the three (1.1%) subjects in the Daytime group who discontinued from the study due to adverse events, one subject (54206) had severe vulvovaginal discomfort that was of highly probable relationship to study drug. Of the seven (2.4%) subjects in the Bedtime group who discontinued study participation due to adverse events, one subject (57507) had a rash of moderate severity on her hands, arms, legs, and trunk that was considered by the investigator to be of probable relationship to study drug. All other events that led to subject discontinuation were unlikely or not related to study drug.

Clinical Reviewer's Comment: Tables 30 and 31 created by the Reviewer using Table 22 in the applicant's study report.

TABLE 30
Subjects Who Discontinued from the Study Due to Adverse Events – Daytime Group
Safety Population

Subject Number	Age	Preferred Term/Verbatim	Study Day of Onset[a]	Duration of AE (Days)	Severity	Relationship to Study Therapy[b]	Outcome
54206	35	Vulvovaginal Discomfort/ Increased Vulvar Burning	1	Cont	Severe	Highly Probable	Recovered
		Vulvovaginal Discomfort/ Increased Vulvovaginal Irritation	1	Cont	Severe	Highly Probable	Recovered
57706	34	Vulvovaginal Discomfort/ Vulvovaginal Burning	14	Cont	Moderate	Not Related	Ongoing
		Vulvovaginal Discomfort/ Vulvovaginal Irritation	15	Cont	Mild	Not Related	Ongoing
66608	53	Vaginitis Bacterial NOS/ Bacterial Vaginosis	20	Cont	Severe	Not Related	Ongoing
		Fungal Infection NOS/ Yeast Infection	20	Cont	Severe	Not Related	Ongoing

TABLE 31
Subjects Who Discontinued from the Study Due to Adverse Events – Bedtime Group
Safety Population

Subject Number	Age	Preferred Term/Verbatim	Study Day of Onset[a]	Duration of AE (Days)	Severity	Relationship to Study Therapy[b]	Outcome
56207	62	Vulvovaginitis NOS/ Recurrent Vulvovaginitis	8	Cont	Mild	Not Related	Ongoing
57507	30	Vulvovaginal Discomfort/ Vulvar Rash	1	Cont	Mild	Not Related	Ongoing
		Rash NOS/ Rash (Hands, Arms, Legs and Truck)	1	6	Moderate	Probable	Recovered
58306	46	Vulvovaginal Discomfort/ Increased Vulvovaginal Symptoms	15	Cont	Severe	Not Related	Ongoing
		Vulvovaginal Discomfort/ Increased Vulvovaginal Erythema	15	Cont	Mild	Not Related	Ongoing
59506	76	Herpes Zoster/Shingles	10	Cont	Severe	Unlikely	Ongoing
60508	63	Breast Infection NOS/ Breast Infection	4	Cont	Moderate	Not Related	Ongoing
64706	41	Vulvovaginal Discomfort/ Vulvovaginal Itching	7	Cont	Moderate	Not Related	Ongoing
		Vulvovaginal Discomfort/ Vulvovaginal Burning	7	Cont	Moderate	Not Related	Ongoing
		Vulvovaginal Discomfort/ Vulvovaginal Erythema	7	Cont	Moderate	Not Related	Ongoing

Subject Number	Age	Preferred Term/Verbatim	Study Day of Onset[a]	Duration of AE (Days)	Severity	Relationship to Study Therapy[b]	Outcome
75107	44	Vulvovaginal Discomfort/ Continuing Vulvovaginal Symptoms	8	13	Moderate	Unlikely	Recovered

[a] Relative to start of therapy (Day 1).
[b] Based on investigator's assessment.

Other Safety Findings – Gynecological Exam

In general, vulvovaginal signs observed during the Admission Visit reduced in severity by the Test-of-Cure Visit in both groups. In the Daytime group, a total of 69 (46.3%) subjects had moderate erythema and 17 (11.4%) subjects had severe erythema at admission; by Test-of-Cure only five (3.4%) subjects had moderate erythema and no subjects had severe erythema. In the Bedtime group, 86 (52.8%) subjects had moderate erythema and 23 (14.1%) subjects had severe erythema at admission; by Test-of-Cure six (3.7%) subjects had moderate erythema and no subjects had severe erythema.

Further reductions in vulvovaginal signs were observed in edema and excoriation. A total of 40 (26.8%) subjects in the Daytime group and 46 (28.2%) subjects in the Bedtime group had moderate edema at admission compared to no subjects in the Daytime group and one (0.6%) subject in the Bedtime group at Test-of-Cure. Severe edema was observed in eight (4.9%) subjects in the Bedtime group, compared to no subjects at Test-of-Cure. A total of 23 (15.4%) subjects in the Daytime group and 18 (11.0%) subjects in the Bedtime group had moderate excoriation at admission, compared to one (0.7%) subject in the Daytime group and no subjects in the Bedtime group at Test-of-Cure. Severe excoriation was observed in three (2.0%) subjects and eight (4.9%) subjects in the Daytime and Bedtime groups, respectively; no subject in either group had severe excoriation at Test-of-Cure.

Other gynecologic observations noted as adverse events (Table 28) included three subjects in the Daytime group and one subject in the Bedtime group with vaginal discharge. In the Daytime group, one subject was observed to have an ovarian cyst and one subject was observed to have a vulval laceration.

Adverse Events by Age and Race

Adverse events reported for female subjects in younger (≤ 64 years) and older age groups (≥ 65 years) by treatment group are shown in Tables 32 and 33 (found in Section 10.3 "Additional Tables"). The majority of subjects were in the younger age group as compared to the older age group (N=554 versus 16 total); therefore differences, if any, seen in adverse events reported for younger and older female subjects are not considered clinically meaningful.

Adverse events reported for female subjects belonging to Caucasian, Black, and Hispanic racial group are shown in Tables 34-36 (found in Section 10.3 "Additional Tables). Subjects of Asian (N=7 total) and "Other" (N=2 total) racial descent, as coded by the applicant, were few in number and adverse events from these subjects were not included in tabular format. Relatively small numbers of subjects were in the Black (N=121) and Hispanic (N=54 total) groups compared to Caucasian (N=386). Differences, if any, seen in adverse events reported for Caucasian, Black, and Hispanic subjects are not considered clinically meaningful.

Reporting of adverse events by age or race is not warranted in the labeling of Monistat 1 Combination Pack.

10.1.31 Overall Summary

This was a multicenter, randomized, investigator-blinded, Phase 3 study of single-dose miconazole nitrate 1200 mg vaginal insert (ovule) in the treatment of VVC in adult, otherwise healthy women. Subjects were randomly assigned to self-administer the ovule either at bedtime (subsequently remaining in bed for at least 30 minutes) or at a subject-determined convenient time during the day (within six hours after arising). Both treatment groups also received a nine-gram tube of 2% miconazole nitrate external vulvar cream to be applied up to twice daily to the vulvar area, as needed for external symptoms, for a maximum of seven days.

The primary efficacy variable for the study was the therapeutic cure rate. A subject was considered a therapeutic cure only if she was both a clinical and mycological cure at the Test-of-Cure Visit (21 to 30 days following intravaginal administration of study drug). If the upper bound of the 95% two-sided confidence interval for the treatment group difference (Daytime minus Bedtime) was less than or equal to 15%, daytime administration would be considered non-inferior to bedtime administration.

The therapeutic cure rates for subjects evaluable for efficacy at the Test-of-Cure Visit were 57.5% (86/149) in the Daytime group and 50.9% (83/163) in the Bedtime group, with a 95% confidence interval of (-4.6%, 18.2%). The lower bound of the 95% confidence interval was greater than -15%; therefore, the daytime administration is non-inferior to bedtime administration.

Mycological cure rates were 70.5% (105/149) versus 63.8% (104/163), and clinical cure rates were 74.5% (111/149) versus 73.6% (120/163) for the Daytime and Bedtime groups, in the Efficacy evaluable population, respectively.

Results for the Intent-to-Treat population were lower but consistent with the Efficacy Evaluable population: 43.5% (121/287) in the Daytime group compared to 35.3% (103/292) in the Bedtime group for the therapeutic cure rates [95% CI (0.1%, 16.4%)]; 50.7% (141/278) compared to 44.5% (130/292) for mycological cure rates; and 70.1% (195/278) compared to 67.1% (196/292) for clinical cure rates, respectively. Clinical and mycological response rates were positively, but weakly, correlated in both the Efficacy Evaluable and Intent-to-Treat populations.

The therapeutic cure rates at the Test-of-Cure Visit in the Efficacy Evaluable populations in the Daytime group were not significantly different between subjects with a low activity level (60.5% [26/43]) compared to a high activity level (56.2% [59/105]) ($p = 0.7154$). Therapeutic cure rates were lower in the Intent-to-Treat population, but also were not significantly different between the low and high activity levels (48.8% [39/80] compared to 43.0% [80/186], $p = 0.4212$).

Comparisons between treatment schedules for the Efficacy Evaluable and Intent-to-Treat populations showed no statistically significant difference between the Daytime and Bedtime groups for the estimated time to relief of itching, burning, and irritation, and for all three symptoms combined.

Differences, if any, seen in the therapeutic cure rates between female subjects in the following groups are not considered clinically meaningful: younger ($\leq$ 64 years) and older adults ($\geq$ 65 years); and Caucasians, Blacks, and Hispanics. No changes to the recommended dosing of Monistat 1 Combination Pack are warranted based on age or race.

Of the 570 safety evaluable subjects, 283 (49.6%) subjects experienced at least one adverse event (143 [51.4%] subjects in the Daytime group and 140 [47.9%] subjects in the Bedtime group).

There were no deaths during the study. There were three serious adverse events (undifferentiated schizophrenia, nausea, and vomiting NOS) reported by two subjects during the study, all of which were considered not related or of unlikely relationship to study drug.

One subject in each group had a treatment-related adverse event (severe vulvovaginal discomfort and rash of moderate severity on hands, arms, legs, and trunk) that lead to study discontinuation.

Treatment-emergent adverse events observed in this study were consistent with the known safety profile of miconazole nitrate. The reproductive system and breast disorders body system was affected most frequently in both treatment groups, primarily consisting of vulvovaginal discomfort (18.7% [52/278] in the Daytime group and 21.6% [63/292] in the Bedtime group),

Most adverse events were mild or moderate in intensity. Thirty-three (11.9%) and 37 (12.7%) adverse events were considered to be severe in intensity in the Daytime and Bedtime groups, respectively. Most severe adverse events in both groups were reports of vulvovaginal discomfort.

In the Daytime group, 34 adverse events were considered by the investigator to be of possible, probable, or highly probable relationship to study drug. The Bedtime group reported 45 adverse events that were considered by the investigator to be of possible, probable, or highly probable relationship to study drug. In both groups, most events with highly probable, probable, or possible relationship to study drug were reports of vulvovaginal discomfort in the reproductive system and breast disorders body system.

Differences, if any, seen in adverse events reported for female subjects in the following groups are not considered clinically meaningful: younger ($\leq$ 64 years) and older adults ($\geq$ 65 years); and

Caucasians, Blacks, and Hispanics. Reporting of adverse events by age or race is not warranted in the labeling of Monistat 1 Combination Pack.

In summary, miconazole nitrate 1200 mg vaginal insert (ovule) and 2% external vulvar cream (Monistat 1 Combination Pack) is safe and effective for daytime use for the treatment of vulvovaginal candidiasis in otherwise healthy adult women.

10.2 Line-by-Line Labeling Review

A line-by-line labeling review was not conducted. The final labeling agreed upon between the FDA and the applicant for the nonprefilled carton and insert and the prefilled carton and insert can be found at: \\cdsesub1\N21308\S_009\2004-08-18.

10.3 Additional Tables from Study CA-P-2343

Adverse events reported for female subjects in younger (16 to 64 years) and older age groups (≥ 65 years) by treatment group are shown in Tables 31 and 32.

Adverse events reported for female subjects belonging to Caucasian, Black, and Hispanic racial group are shown in Tables 33-35.

Clinical Reviewer's Comment: Tables 32 and 33 were adapted by the Reviewer from the applicant's submission dated August 11, 2004. Tables 34-36 can be found in the applicant's submission dated August 17, 2004.

TABLE 32
Incidence of Adverse Events Summarized by Body System and Preferred Term
Subjects Aged 16 to 64 Years
Safety Population

	DAYTIME MONISTAT-1 (N = 272)		BEDTIME MONISTAT-1 (N = 282)	
BODY SYSTEM/PRIMARY TERM	n	(%)	n	(%)
TOTAL SUBJECTS REPORTING ADVERSE EVENTS	140	(51.5)	132	(46.8)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	71	(26.1)	72	(25.5)
VULVOVAGINAL DISCOMFORT	49	(18.0)	59	(20.9)
DYSMENORRHOEA	9	(3.3)	10	(3.5)
GENITAL PRURITUS FEMALE	5	(1.8)	2	(0.7)
VAGINAL IRRITATION	4	(1.5)	1	(0.4)
VAGINAL DISCHARGE	3	(1.1)	1	(0.4)
METRORRHAGIA	2	(0.7)	2	(0.7)
PELVIC PAIN NOS	2	(0.7)	2	(0.7)
VULVOVAGINAL DISORDER NOS	2	(0.7)	2	(0.7)
MENSES DELAYED	1	(0.4)	1	(0.4)
OVARIAN CYST	1	(0.4)	0	
VULVAL LACERATION	1	(0.4)	0	
MENSTRUATION IRREGULAR	0		1	(0.4)
PREMENSTRUAL SYNDROME	0		1	(0.4)
VAGINAL HAEMORRHAGE	0		3	(1.1)
NERVOUS SYSTEM DISORDERS	39	(14.3)	39	(13.8)
HEADACHE	39	(14.3)	34	(12.1)
SINUS HEADACHE	1	(0.4)	3	(1.1)
SOMNOLENCE	1	(0.4)	0	
DIZZINESS	0		2	(0.7)
DYSGEUSIA	0		1	(0.4)
MIGRAINE NOS	0		2	(0.7)
INFECTIONS AND INFESTATIONS	31	(11.4)	33	(11.7)
FUNGAL INFECTION NOS	5	(1.8)	2	(0.7)
SINUSITIS NOS	5	(1.8)	5	(1.8)
VAGINITIS BACTERIAL NOS	5	(1.8)	4	(1.4)
VAGINOSIS FUNGAL NOS	3	(1.1)	0	
HERPES SIMPLEX	2	(0.7)	0	
NASOPHARYNGITIS	2	(0.7)	5	(1.8)
URINARY TRACT INFECTION NOS	2	(0.7)	3	(1.1)
BLADDER INFECTION NOS	1	(0.4)	0	
HERPES ZOSTER	1	(0.4)	0	
PHARYNGITIS	1	(0.4)	0	
PHARYNGITIS STREPTOCOCCAL	1	(0.4)	0	
SINUSITIS ACUTE NOS	1	(0.4)	0	
VULVOVAGINITIS NOS	1	(0.4)	1	(0.4)
CANDIDAL INFECTION NOS	1	(0.4)	0	
BRONCHIAL INFECTION	1	(0.4)	0	
BREAST INFECTION NOS	0		1	(0.4)
CELLULITIS	0		2	(0.7)
EAR INFECTION NOS	0		1	(0.4)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 32 continued
Incidence of Adverse Events Summarized by Body System and Preferred Term
Subjects Aged 16 to 64 Years
Safety Population

	DAYTIME MONISTAT-1 (N = 272)		BEDTIME MONISTAT-1 (N = 282)	
BODY SYSTEM/PRIMARY TERM	n	(%)	n	(%)
INFECTIONS AND INFESTATIONS (CONT.)				
FOLLICULITIS	0		1	(0.4)
PYELONEPHRITIS NOS	0		1	(0.4)
SKIN FUNGAL INFECTION NOS	0		1	(0.4)
TOOTH ABSCESS	0		1	(0.4)
UPPER RESPIRATORY TRACT INFECTION NOS	0		6	(2.1)
VAGINITIS	0		1	(0.4)
ORAL INFECTION	0		1	(0.4)
OTITIS EXTERNA NOS	0		1	(0.4)
EAR INFECTION STAPHYLOCOCCAL	0		1	(0.4)
GASTROINTESTINAL DISORDERS	21	(7.7)	28	(9.9)
DIARRHOEA NOS	6	(2.2)	5	(1.8)
ABDOMINAL PAIN NOS	3	(1.1)	5	(1.8)
CONSTIPATION	3	(1.1)	0	
DYSPEPSIA	3	(1.1)	3	(1.1)
TOOTHACHE	3	(1.1)	2	(0.7)
ABDOMINAL DISCOMFORT	2	(0.7)	1	(0.4)
ABDOMINAL DISTENSION	2	(0.7)	0	
NAUSEA	2	(0.7)	7	(2.5)
ABDOMINAL PAIN UPPER	1	(0.4)	2	(0.7)
LOOSE STOOLS	1	(0.4)	0	
VOMITING NOS	1	(0.4)	2	(0.7)
DENTAL DISCOMFORT	1	(0.4)	0	
ABDOMINAL PAIN LOWER	0		2	(0.7)
FLATULENCE	0		1	(0.4)
GASTROOESOPHAGEAL REFLUX DISEASE	0		3	(1.1)
GASTROINTESTINAL UPSET	0		1	(0.4)
HAEMORRHOIDS	0		1	(0.4)
ORAL PAIN	0		1	(0.4)
PRURITUS ANI	0		1	(0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14	(5.1)	11	(3.9)
COUGH	5	(1.8)	1	(0.4)
PHARYNGOLARYNGEAL PAIN	3	(1.1)	6	(2.1)
UPPER RESPIRATORY TRACT CONGESTION	3	(1.1)	0	
ASTHMA NOS	1	(0.4)	0	
BRONCHITIS NOS	1	(0.4)	2	(0.7)
NASAL CONGESTION	1	(0.4)	4	(1.4)
NASAL PASSAGE IRRITATION	1	(0.4)	0	
RHINORRHOEA	1	(0.4)	0	
POSTNASAL DRIP	0		1	(0.4)
RHINITIS NOS	0		1	(0.4)
SINUS PAIN	0		1	(0.4)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 32 continued
Incidence of Adverse Events Summarized by Body System and Preferred Term
Subjects Aged 16 to 64 Years
Safety Population

	DAYTIME MONISTAT-1 (N = 272)		BEDTIME MONISTAT-1 (N = 282)	
BODY SYSTEM/PRIMARY TERM	n	(%)	n	(%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10	(3.7)	3	(1.1)
PYREXIA	3	(1.1)	1	(0.4)
FATIGUE	2	(0.7)	1	(0.4)
OEDEMA NOS	2	(0.7)	0	
APPLICATION SITE PAIN	1	(0.4)	0	
INFLUENZA LIKE ILLNESS	1	(0.4)	0	
OEDEMA PERIPHERAL	1	(0.4)	0	
PAIN NOS	1	(0.4)	0	
HANGOVER	0		1	(0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	10	(3.7)	23	(8.2)
BACK PAIN	4	(1.5)	10	(3.5)
PAIN IN EXTREMITY	2	(0.7)	1	(0.4)
ARTHRALGIA	1	(0.4)	4	(1.4)
MUSCLE CRAMP	1	(0.4)	2	(0.7)
NECK PAIN	1	(0.4)	3	(1.1)
PAIN IN JAW	1	(0.4)	0	
MUSCULOSKELETAL DISCOMFORT	1	(0.4)	0	
CHEST WALL PAIN	0		1	(0.4)
MYALGIA	0		4	(1.4)
TENDONITIS	0		1	(0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8	(2.9)	6	(2.1)
ERYTHEMA	4	(1.5)	3	(1.1)
DERMATITIS CONTACT	1	(0.4)	0	
RASH NOS	1	(0.4)	2	(0.7)
RASH PRURITIC	1	(0.4)	0	
SWEATING INCREASED	1	(0.4)	0	
URTICARIA NOS	0		1	(0.4)
PSYCHIATRIC DISORDERS	7	(2.6)	11	(3.9)
INSOMNIA	4	(1.5)	8	(2.8)
DEPRESSION	2	(0.7)	0	
ABNORMAL DREAMS	1	(0.4)	0	
SLEEP DISORDER NOS	0		2	(0.7)
SCHIZOPHRENIA, UNDIFFERENTIATED TYPE	0		1	(0.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6	(2.2)	0	
EXCORIATION	4	(1.5)	0	
JOINT SPRAIN	1	(0.4)	0	
LIMB INJURY NOS	1	(0.4)	0	
METABOLISM AND NUTRITION DISORDERS	2	(0.7)	1	(0.4)
DIABETES MELLITUS NOS	1	(0.4)	0	
HYPERCHOLESTEROLAEMIA	1	(0.4)	0	

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 32 continued
Incidence of Adverse Events Summarized by Body System and Preferred Term
Subjects Aged 16 to 64 Years
Safety Population

BODY SYSTEM/PRIMARY TERM	DAYTIME MONISTAT-1 (N = 272) n	(%)	BEDTIME MONISTAT-1 (N = 282) n	(%)
METABOLISM AND NUTRITION DISORDERS (CONT.)				
HYPERTRIGLYCERIDAEMIA	1	(0.4)	0	
ANOREXIA	0		1	(0.4)
VASCULAR DISORDERS	2	(0.7)	0	
FLUSHING	1	(0.4)	0	
HYPERTENSION NOS	1	(0.4)	0	
EYE DISORDERS	1	(0.4)	0	
EYE PRURITUS	1	(0.4)	0	
IMMUNE SYSTEM DISORDERS	1	(0.4)	2	(0.7)
HYPERSENSITIVITY NOS	1	(0.4)	1	(0.4)
SEASONAL ALLERGY	0		1	(0.4)
RENAL AND URINARY DISORDERS	1	(0.4)	4	(1.4)
DYSURIA	1	(0.4)	2	(0.7)
CYSTITIS NOS	0		1	(0.4)
MICTURITION URGENCY	0		1	(0.4)
EAR AND LABYRINTH DISORDERS	0		3	(1.1)
EAR PAIN	0		1	(0.4)
MOTION SICKNESS	0		1	(0.4)
SENSATION OF BLOCK IN EAR	0		1	(0.4)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 33
Incidence of Adverse Events Summarized by Body System and Preferred Term
Subjects Aged ≥ 65 Years
Safety Population

BODY SYSTEM/PRIMARY TERM	DAYTIME MONISTAT-1 (N = 6) n	(%)	BEDTIME MONISTAT-1 (N = 10) n	(%)
TOTAL SUBJECTS REPORTING ADVERSE EVENTS	3	(50.0)	8	(80.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3	(50.0)	5	(50.0)
VULVOVAGINAL DISCOMFORT	3	(50.0)	4	(40.0)
GENITAL PRURITUS FEMALE	1	(16.7)	2	(20.0)
VAGINAL IRRITATION	0		1	(10.0)
NERVOUS SYSTEM DISORDERS	1	(16.7)	0	
HEADACHE	1	(16.7)	0	
INFECTIONS AND INFESTATIONS	0		2	(20.0)
HERPES SIMPLEX	0		1	(10.0)
HERPES ZOSTER	0		1	(10.0)
RENAL AND URINARY DISORDERS	0		1	(10.0)
HYPERTONIC BLADDER	0		1	(10.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0		1	(10.0)
RHINORRHOEA	0		1	(10.0)
SNEEZING	0		1	(10.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 34
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Caucasian Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
TOTAL SUBJECTS REPORTING ADVERSE EVENTS	29	(15.3)	46	(24.3)	25	(13.2)	0	(0.0)	100	(52.9)	33	(16.8)	36	(18.3)	29	(14.7)	0	(0.0)	98	(49.7)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	20	(10.6)	18	(9.5)	13	(6.9)	0	(0.0)	51	(27.0)	21	(10.7)	17	(8.6)	14	(7.1)	0	(0.0)	52	(26.4)
VULVOVAGINAL DISCOMFORT	12	(6.3)	11	(5.8)	13	(6.9)	0	(0.0)	36	(19.0)	15	(7.6)	15	(7.6)	12	(6.1)	0	(0.0)	42	(21.3)
DYSMENORRHOEA	4	(2.1)	3	(1.6)	0	(0.0)	0	(0.0)	7	(3.7)	3	(1.5)	5	(2.5)	0	(0.0)	0	(0.0)	8	(4.1)
GENITAL PRURITUS FEMALE	3	(1.6)	2	(1.1)	0	(0.0)	0	(0.0)	5	(2.6)	4	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(2.0)
METRORRHAGIA	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)
PELVIC PAIN NOS	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)	2	(1.0)
VULVOVAGINAL DISORDER NOS	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	2	(1.1)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
MENSES DELAYED	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
OVARIAN CYST	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VAGINAL IRRITATION	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
MENSTRUATION IRREGULAR	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
PREMENSTRUAL SYNDROME	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
VAGINAL HAEMORRHAGE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	3	(1.5)
NERVOUS SYSTEM DISORDERS	10	(5.3)	13	(6.9)	7	(3.7)	0	(0.0)	30	(15.9)	13	(6.6)	11	(5.6)	5	(2.5)	0	(0.0)	29	(14.7)
HEADACHE	10	(5.3)	13	(6.9)	7	(3.7)	0	(0.0)	30	(15.9)	12	(6.1)	10	(5.1)	4	(2.0)	0	(0.0)	26	(13.2)
SINUS HEADACHE	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.0)
SOMNOLENCE	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
DIZZINESS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.0)
MIGRAINE NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
INFECTIONS AND INFESTATIONS	7	(3.7)	14	(7.4)	1	(0.5)	0	(0.0)	22	(11.6)	12	(6.1)	7	(3.6)	6	(3.0)	0	(0.0)	25	(12.7)
SINUSITIS NOS	0	(0.0)	3	(1.6)	1	(0.5)	0	(0.0)	4	(2.1)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
INFECTIONS AND INFESTATIONS (CONT.)																				
FUNGAL INFECTION NOS	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HERPES SIMPLEX	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
URINARY TRACT INFECTION NOS	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	2	(1.0)	1	(0.5)	0	(0.0)	0	(0.0)	3	(1.5)
VAGINITIS BACTERIAL NOS	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	2	(1.0)
VAGINOSIS FUNGAL NOS	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
BLADDER INFECTION NOS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NASOPHARYNGITIS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	3	(1.5)	0	(0.0)	0	(0.0)	4	(2.0)
PHARYNGITIS	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
PHARYNGITIS STREPTOCOCCAL	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SINUSITIS ACUTE NOS	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VULVOVAGINITIS NOS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
CANDIDAL INFECTION NOS	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
BRONCHIAL INFECTION	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
BREAST INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
CELLULITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.0)
EAR INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
FOLLICULITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
HERPES ZOSTER	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
PYELONEPHRITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
SKIN FUNGAL INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
TOOTH ABSCESS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
UPPER RESPIRATORY TRACT INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.5)	0	(0.0)	1	(0.5)	0	(0.0)	4	(2.0)
VAGINITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
ORAL INFECTION	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
EAR INFECTION STAPHYLOCOCCAL	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 34 continued
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Caucasian Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
GASTROINTESTINAL DISORDERS	6	(3.2)	7	(3.7)	4	(2.1)	0	(0.0)	17	(9.0)	9	(4.6)	11	(5.6)	3	(1.5)	0	(0.0)	23	(11.7)
DIARRHOEA NOS	2	(1.1)	2	(1.1)	1	(0.5)	0	(0.0)	5	(2.6)	1	(0.5)	4	(2.0)	0	(0.0)	0	(0.0)	5	(2.5)
ABDOMINAL PAIN NOS	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	3	(1.6)	1	(0.5)	3	(1.5)	0	(0.0)	0	(0.0)	4	(2.0)
DYSPEPSIA	1	(0.5)	2	(1.1)	0	(0.0)	0	(0.0)	3	(1.6)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)
ABDOMINAL DISCOMFORT	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	2	(1.1)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
CONSTIPATION	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NAUSEA	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	4	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(2.0)
TOOTHACHE	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)	2	(1.0)
ABDOMINAL DISTENSION	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ABDOMINAL PAIN UPPER	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	2	(1.0)
LOOSE STOOLS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VOMITING NOS	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)
DENTAL DISCOMFORT	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ABDOMINAL PAIN LOWER	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
FLATULENCE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
GASTROOESOPHAGEAL REFLUX DISEASE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)	0	(0.0)	1	(0.5)	0	(0.0)	3	(1.5)
GASTROINTESTINAL UPSET	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
HAEMORRHOIDS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
ORAL PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
PRURITUS ANI	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4	(2.1)	6	(3.2)	0	(0.0)	0	(0.0)	10	(5.3)	5	(2.5)	10	(5.1)	2	(1.0)	0	(0.0)	17	(8.6)
BACK PAIN	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)	4	(2.1)	3	(1.5)	3	(1.5)	1	(0.5)	0	(0.0)	7	(3.6)
PAIN IN EXTREMITY	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
ARTHRALGIA	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(1.0)	0	(0.0)	0	(0.0)	3	(1.5)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (CONT.)																				
MUSCLE CRAMP	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NECK PAIN	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	2	(1.0)	1	(0.5)	0	(0.0)	3	(1.5)
PAIN IN JAW	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
MUSCULOSKELETAL DISCOMFORT	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
MYALGIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(2.0)	0	(0.0)	0	(0.0)	4	(2.0)
TENDONITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5	(2.6)	5	(2.6)	0	(0.0)	0	(0.0)	10	(5.3)	4	(2.0)	2	(1.0)	3	(1.5)	0	(0.0)	9	(4.6)
COUGH	2	(1.1)	2	(1.1)	0	(0.0)	0	(0.0)	4	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
PHARYNGOLARYNGEAL PAIN	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	3	(1.5)	0	(0.0)	2	(1.0)	0	(0.0)	5	(2.5)
UPPER RESPIRATORY TRACT CONGESTION	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ASTHMA NOS	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NASAL CONGESTION	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(1.0)	0	(0.0)	0	(0.0)	3	(1.5)
NASAL PASSAGE IRRITATION	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RHINORRHOEA	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
RHINITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
SINUS PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
SNEEZING	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3	(1.6)	1	(0.5)	2	(1.1)	0	(0.0)	6	(3.2)	2	(1.0)	0	(0.0)	1	(0.5)	0	(0.0)	3	(1.5)
PYREXIA	2	(1.1)	1	(0.5)	0	(0.0)	0	(0.0)	3	(1.6)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
APPLICATION SITE PAIN	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 34 continued
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Caucasian Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (CONT.)																				
FATIGUE	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
OEDEMA PERIPHERAL	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
PAIN NOS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HANGOVER	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4	(2.1)	0	(0.0)	1	(0.5)	0	(0.0)	5	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
EXCORIATION	2	(1.1)	0	(0.0)	1	(0.5)	0	(0.0)	3	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
JOINT STRAIN	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
LIMB INJURY NOS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
PSYCHIATRIC DISORDERS	2	(1.1)	2	(1.1)	1	(0.5)	0	(0.0)	5	(2.6)	6	(3.0)	4	(2.0)	1	(0.5)	0	(0.0)	11	(5.6)
DEPRESSION	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
INSOMNIA	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.1)	4	(2.0)	4	(2.0)	0	(0.0)	0	(0.0)	8	(4.1)
ABNORMAL DREAMS	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SLEEP DISORDER NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)
SCHIZOPHRENIA, UNDIFFERENTIATED TYPE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	(1.1)	0	(0.0)	2	(1.1)	0	(0.0)	4	(2.1)	1	(0.5)	2	(1.0)	0	(0.0)	0	(0.0)	3	(1.5)
DERMATITIS CONTACT	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ERYTHEMA	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	2	(1.0)
RASH PRURITIC	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SWEATING INCREASED	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
URTICARIA NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

	DAYTIME MONISTAT-1 (N=189)										BEDTIME MONISTAT-1 (N=197)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
IMMUNE SYSTEM DISORDERS	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	2	(1.0)
HYPERSENSITIVITY NOS	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
SEASONAL ALLERGY	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
METABOLISM AND NUTRITION DISORDERS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
HYPERCHOLESTEROLAEMIA	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HYPERTRIGLYCERIDAEMIA	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ANOREXIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
RENAL AND URINARY DISORDERS	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(1.0)	1	(0.5)	0	(0.0)	4	(2.0)
DYSURIA	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	2	(1.0)
CYSTITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
HYPERTONIC BLADDER	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
EAR AND LABYRINTH DISORDERS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	3	(1.5)
EAR PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
MOTION SICKNESS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)
SENSATION OF BLOCK IN EAR	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 35
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Black Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=61)										REDTIME MONISTAT-1 (N=60)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
TOTAL SUBJECTS REPORTING ADVERSE EVENTS	10	(16.4)	15	(24.6)	6	(9.8)	0	(0.0)	31	(50.8)	15	(25.0)	8	(13.3)	4	(6.7)	0	(0.0)	27	(45.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	6	(9.8)	7	(11.5)	4	(6.6)	0	(0.0)	17	(27.9)	12	(20.0)	3	(5.0)	2	(3.3)	0	(0.0)	17	(28.3)
VULVOVAGINAL DISCOMFORT	4	(6.6)	6	(9.8)	3	(4.9)	0	(0.0)	13	(21.3)	10	(16.7)	2	(3.3)	2	(3.3)	0	(0.0)	14	(23.3)
VAGINAL DISCHARGE	1	(1.6)	2	(3.3)	0	(0.0)	0	(0.0)	3	(4.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VAGINAL IRRITATION	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.3)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
DYSMENORRHOEA	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.6)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
GENITAL PRURITUS FEMALE	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VULVOVAGINAL DISORDER NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
INFECTIONS AND INFESTATIONS	2	(3.3)	3	(4.9)	1	(1.6)	0	(0.0)	6	(9.8)	3	(5.0)	2	(3.3)	0	(0.0)	0	(0.0)	5	(8.3)
FUNGAL INFECTION NOS	1	(1.6)	1	(1.6)	1	(1.6)	0	(0.0)	3	(4.9)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
VAGINITIS BACTERIAL NOS	0	(0.0)	1	(1.6)	1	(1.6)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SINUSITIS NOS	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
VAGINOSIS FUNGAL NOS	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NASOPHARYNGITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
UPPER RESPIRATORY TRACT INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3	(4.9)	0	(0.0)	1	(1.6)	0	(0.0)	4	(6.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
OEDEMA NOS	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
FATIGUE	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
INFLUENZA LIKE ILLNESS	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NERVOUS SYSTEM DISORDERS	2	(3.3)	1	(1.6)	0	(0.0)	1	(1.6)	4	(6.6)	2	(3.3)	3	(5.0)	1	(1.7)	0	(0.0)	6	(10.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

	DAYTIME MONISTAT-1 (N=61)										REDTIME MONISTAT-1 (N=60)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
NERVOUS SYSTEM DISORDERS (CONT.)																				
HEADACHE	2	(3.3)	1	(1.6)	0	(0.0)	1	(1.6)	4	(6.6)	1	(1.7)	2	(3.3)	1	(1.7)	0	(0.0)	4	(6.7)
DYSGEUSIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
MIGRAINE NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
SINUS HEADACHE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
GASTROINTESTINAL DISORDERS	0	(0.0)	2	(3.3)	1	(1.6)	0	(0.0)	3	(4.9)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
CONSTIPATION	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
DIARRHOEA NOS	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
TOOTHACHE	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
ABDOMINAL PAIN NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
NAUSEA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1.6)	2	(3.3)	0	(0.0)	0	(0.0)	3	(4.9)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
BRONCHITIS NOS	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
COUGH	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
PHARYNGOLARYNGEAL PAIN	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
NASAL CONGESTION	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
POSTNASAL DRIP	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	(0.0)	3	(4.9)	0	(0.0)	0	(0.0)	3	(4.9)	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	2	(3.3)
ERYTHEMA	0	(0.0)	3	(4.9)	0	(0.0)	0	(0.0)	3	(4.9)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
RASH NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)
PSYCHIATRIC DISORDERS	1	(1.6)	1	(1.6)	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

TABLE 35 continued
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Black Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=61)										BEDTIME MONISTAT-1 (N=60)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
PSYCHIATRIC DISORDERS (CONT.)																				
INSOMNIA	1	(1.6)	1	(1.6)	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VASCULAR DISORDERS	1	(1.6)	1	(1.6)	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
FLUSHING	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HYPERTENSION NOS	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
EYE DISORDERS	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
EYE PRURITUS	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
EXCORIATION	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	1	(1.7)	0	(0.0)	2	(3.3)
BACK PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	1	(1.7)
MUSCLE CRAMP	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)	1	(1.7)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

APPEARS THIS WAY
ON ORIGINAL

TABLE 36
Incidence of Adverse Events Summarized by Body System, Preferred Term, and Severity
Black Subjects
Safety Population

	DAYTIME MONISTAT-1 (N=26)										BEDTIME MONISTAT-1 (N=28)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
TOTAL SUBJECTS REPORTING ADVERSE EVENTS	6	(23.1)	4	(15.4)	2	(7.7)	0	(0.0)	12	(46.2)	4	(14.3)	4	(14.3)	3	(10.7)	0	(0.0)	11	(39.3)
NERVOUS SYSTEM DISORDERS	4	(15.4)	1	(3.8)	1	(3.8)	0	(0.0)	6	(23.1)	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	2	(7.1)
HEADACHE	4	(15.4)	1	(3.8)	1	(3.8)	0	(0.0)	6	(23.1)	1	(3.6)	1	(3.6)	0	(0.0)	0	(0.0)	2	(7.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3	(11.5)	2	(7.7)	1	(3.8)	0	(0.0)	6	(23.1)	3	(10.7)	0	(0.0)	2	(7.1)	0	(0.0)	5	(17.9)
VULVOVAGINAL DISCOMFORT	2	(7.7)	0	(0.0)	1	(3.8)	0	(0.0)	3	(11.5)	3	(10.7)	0	(0.0)	2	(7.1)	0	(0.0)	5	(17.9)
DYSMENORRHOEA	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VULVAL LACERATION	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VAGINAL IRRITATION	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
INFECTIONS AND INFESTATIONS	2	(7.7)	1	(3.8)	0	(0.0)	0	(0.0)	3	(11.5)	2	(7.1)	2	(7.1)	1	(3.6)	0	(0.0)	5	(17.9)
HERPES ZOSTER	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NASOPHARYNGITIS	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
VAGINITIS BACTERIAL NOS	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	2	(7.1)	0	(0.0)	0	(0.0)	2	(7.1)
FUNGAL INFECTION NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)
SINUSITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(3.6)
OTITIS EXTERNA NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)
GASTROINTESTINAL DISORDERS	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
ABDOMINAL DISTENSION	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
DYSPEPSIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
NAUSEA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
METABOLISM AND NUTRITION DISORDERS	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

	DAYTIME MONISTAT-1 (N=26)										BEDTIME MONISTAT-1 (N=28)									
	MILD		MODERATE		SEVERE		UNKNOWN		TOTAL		MILD		MODERATE		SEVERE		UNKNOWN		TOTAL	
ADVERSE EVENTS BY BODY SYSTEM	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
METABOLISM AND NUTRITION DISORDERS (CONT.)																				
DIABETES MELLITUS NOS	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(3.6)
UPPER RESPIRATORY TRACT CONGESTION	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
BRONCHITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(3.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RASH NOS	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	2	(7.1)	0	(0.0)	0	(0.0)	3	(10.7)
ARTHRALGIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
BACK PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
CHEST WALL PAIN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	1	(3.6)
MUSCLE CRAMP	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)
RENAL AND URINARY DISORDERS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(3.6)
MICTURITION URGENCY	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.6)	0	(0.0)	1	(3.6)

NOTE: PERCENTAGES ARE THE PROPORTIONS OF SUBJECTS WITHIN THAT CATEGORY

REFERENCES

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-308 S-009
Drug Name:	Monistat 1 Combination Pack (miconazole nitrate vaginal insert 1200 mg and miconazole nitrate cream 2%)
Indication(s):	Treatment of vulvovaginal candidiasis and relief of external vulvar irritation
Applicant:	Personal Products Company
Date(s):	Submission date: 12/3/03
	User Fee date: 10/3/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Karen M. Higgins, Sc.D.
Concurring Reviewers:	Mohammad Huque, Ph.D.
Medical Division:	Division of Special Pathogens and Immunologic Drug Products (DSPIDP) and the Division of Over the Counter Drug Products (OTC)
Clinical Team:	Medical Reviewer: Joette Meyer, Pharm.D.
	Medical Team Leader: Steven Gitterman, M.D.
Project Manager:	Anne Marie Homonnay Weikel (DSPIDP)
	Leah Cutter (OTC)

Keywords: active control/non-inferiority, randomization

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Personal Products Company, the sponsor, conducted one phase III study to show that daytime administration of the Monistat Ovule as part of the Monistat 1 Combination Pack has similar efficacy to bedtime administration of the ovule, the currently approved administration time. Additionally they recorded activity level to ensure that moderate to vigorous activity within 4 hours of administration would not reduce the efficacy of the product.

The results of the phase III study showed that efficacy of the daytime administration is non-inferior to the bedtime administration, using a non-inferiority margin of 15%. Furthermore, efficacy does not seem to be reduced in those subjects obtaining moderate to vigorous activity within 4 hours of administration compared to those subjects administering the product at bedtime.

The results of the study support the change in labeling removing the words "at bedtime".

1.2 Brief Overview of Clinical Studies

Miconazole nitrate 1200 mg vaginal ovule and 2% external vulvar cream was approved as a prescription drug product in 1999 for the treatment of vulvovaginal candidiasis (VVC). It was subsequently approved for OTC sale in 2001 under the name Monistat 1 Combination Pack (NDA 21-308). Labeling instructions for this product stated that it should be inserted at bedtime insuring that the product would remain in place. The sponsor is proposing that the words "at bedtime" be removed from the label of this product, therefore, not limiting the administration of this product to bedtime use only. The sponsor conducted one phase III trial, CA-P-2343, "A multi-center, randomized, parallel-group, investigator-blinded study to compare the safety and efficacy of MONISTAT® 1 Combination Pack in Bedtime versus Daytime administration," to compare daytime administration with bedtime administration. Level of activity of the subjects in the daytime group after administration was captured in this study.

The primary objective of study CA-P-2343 was to assess both the safety and efficacy of daytime administration of Monistat 1 Ovule compared to bedtime administration. The study was multicenter, randomized, parallel, and investigator-blind. Approximately 520 subjects were to be enrolled. Subjects were randomized to either bedtime or daytime administration of the Monistat ovule insert (single dose). Subjects assigned to bedtime administration were to remain in bed for at least 30 minutes after dosing. Subjects assigned to daytime administration were to administer the ovule at a subject-determined convenient time during the day but within 6 hours after arising. Both groups were permitted to use miconazole nitrate (2%) external vulvar cream twice daily for a maximum of seven days as needed. The primary efficacy variable is therapeutic cure rate measured at the test of cure visit, 21-30 days after insertion of the ovule. A subject is

considered a therapeutic cure if she is both a clinical cure and a mycological cure. Non-inferiority will be shown if the two-sided 95% confidence interval for the difference (daytime-bedtime) in rates of therapeutic cure excludes the non-inferiority margin of -15%.

1.3 Statistical Issues and Findings

The following table reports the results of the primary endpoint, therapeutic cure, analyzed using both the efficacy evaluable and the intent-to-treat patient populations. Both of these analyses show non-inferiority, using a non-inferiority margin of 15% as defined in the protocol, since the confidence intervals exclude -15%.

Table 1: Sponsor's Primary Analysis of Therapeutic Cure

Therapeutic cure rates /Group	**Daytime Monistat 1 n/N**	**(%)**	**Bedtime Monistat 1 n/N**	**(%)**	**95% Confidence Interval***
Efficacy Evaluable	86/149	(57.7)	83/163	(50.9)	[-4.6, 18.2]
Intent to Treat	121/278	(43.5)	103/292	(35.3)	[0.1, 16.4]

* 95% confidence intervals calculated as Daytime – Bedtime
Source: from Sponsor's table 8.1 and 8.2

The following table report efficacy by activity level obtained. Response rates for all activity levels are similar to those seen with the bedtime group. However, note that these subgroups are based on post-randomization information. Therefore inclusion into these groups may not be independent of outcome. For example, it could be the case that patients in the vigorous group felt well and then chose to undertake a vigorous activity.

Table 2: Response by Activity Level for Efficacy Evaluable Population

	Therapeutic Cure rates		**Micro Cure rates**		**Clinical Cure rates**	
Group/response	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Daytime by activity level						
Missing	1/1	(100)	1/1	(100)	1/1	(100)
Inactive	4/4	(100)	4/4	(100)	4/4	(100)
Mild	22/39	(56.4)	31/39	(79.5)	26/39	(66.7)
Moderate	38/75	(50.7)	48/75	(64.0)	54/75	(72.0)
Vigorous	21/30	(70.0)	21/30	(70.0)	26/30	(86.7)
Bedtime	83/163	(50.9)	104/163	(63.8)	120/163	(73.6)

Source: Reviewer's analysis

2. INTRODUCTION

2.1 Overview

Miconazole nitrate 1200 mg vaginal ovule and 2% external vulvar cream was approved as a prescription drug product in 1999 for the treatment of vulvovaginal candidiasis (VVC). It was subsequently approved for OTC sale in 2001 under the name Monistat 1 Combination Pack (NDA 21-308). Labeling instructions for this product stated that it should be inserted at bedtime insuring that the product would remain in place. However, the formulation of the vaginal ovule which consists of 1200 mg of miconazole nitrate in ~ ml of bioadhesive oil suspension filled into a water soluble soft gelatin shell will adhere to the moist vaginal membrane and react with vaginal fluid. This will cause the formulation to remain in situ regardless of the activity level after administration, allowing for administration during the day or at bedtime.

The sponsor conducted one phase III trial, CA-P-2343, "A multi-center, randomized, parallel-group, investigator-blinded study to compare the safety and efficacy of MONISTAT® 1 Combination Pack in Bedtime versus Daytime administration," to ensure that the clinical efficacy from daytime administration is not worse than that for bedtime administration. Level of activity of the subjects in the daytime group after administration was captured in this study. The sponsor is proposing that the words "at bedtime" be removed from the label of this product, therefore, not limiting the administration of this product to bedtime use only.

This submission was submitted to the Division of Over the Counter Drug Products. The medical officer, statistician, and microbiologist reviewing the phase III study are from the Division of Special Pathogens and Immunologic Drug Products.

2.2 Data Sources

Electronic data was not originally submitted with this NDA. The Agency requested that the sponsor submit all the data from the Phase III study electronically. They agreed and submitted the data on 1/20/04. This data was found to be in an incorrect format. The data was resubmitted on 2/13/04 in the correct format.

The data sets are stored in the electronic document room in the following location:
\\Cdsesub1\N21308\S_009\2004-02-13\crt\datasets\CA-P-2343
All data sets were found to be of good quality, clearly documented and well organized.

3. STATISTICAL EVALUATION

This section will review the efficacy and briefly the safety of study CA-P-2343, "A multi-center, randomized, parallel-group, investigator-blinded study to compare the safety and efficacy of MONISTAT® 1 Combination Pack in Bedtime versus Daytime administration."

3.1 Evaluation of Efficacy

3.1.1 Study Objectives and Design

The primary objective of study CA-P-2343 was to assess both the safety and efficacy of daytime administration of Monistat 1 Ovule compared to bedtime administration. The study was multicenter, randomized, parallel, and investigator-blind. Approximately 520 subjects were to be enrolled. Subjects were randomized to either bedtime or daytime administration of the Monistat ovule insert (single dose). Subjects assigned to bedtime administration were to remain in bed for at least 30 minutes after dosing. Subjects assigned to daytime administration were to administer the ovule at a subject-determined convenient time during the day but within 6 hours after arising. Both groups were permitted to use miconazole nitrate (2%) external vulvar cream twice daily for a maximum of seven days as needed.

A post-therapy telephone contact was to be made 7-10 days following administration of the ovule and the test of cure visit was to be conducted 21 – 30 days following study drug use. If during the post-therapy telephone contact, the subject's clinical response was inadequate, the subject was to return to the office for an interim visit.

Reviewer's comment: Note that the number of patients with an interim visit was similar between the two treatment groups. Twelve patients (4.3% of all randomized daytime patients) in the daytime group and 14 patients (4.8% of all randomized bedtime patients) in the bedtime group had an interim visit. About half of these patients were still experiencing symptoms.

Daily diary cards were given to all subjects. Subjects were to record the date and exact time of insertion of the ovule insert. Study day 1 was defined as the day of insertion. Subjects were to record symptoms at baseline, 30 minutes following insertion, and twice daily for 7 days. Subjects were also to record use of external cream along with any other vulvovaginal products or additional medication. In addition, subjects assigned to the daytime regimen were to record their daily activity at 1 hour intervals from the time of administration of study drug up to 4 hours following insertion of the ovule. Each activity was categorized as either inactive, mild activity, moderate activity, or vigorous activity. If a subject performed more than one activity within the one hour interval, the type of activity for the activity in which the subject spent the majority of the time doing during that hour would be recorded. A minimum of 20% of subjects assigned to the daytime group were to obtain a vigorous activity level and 80% were to obtain a moderate or vigorous level of activity for at least one of the 4 hours following administration.

The primary efficacy variable is therapeutic cure rate measured at the test of cure visit, 21-30 days after insertion of the ovule. A subject is considered a therapeutic cure if she is both a clinical cure and a mycological cure.

Clinical response is based on the signs and symptoms of VVC from admission to the test of cure visit. To be considered a cure all signs and symptoms that were mild or moderate at admission would need to be absent at the test of cure visit and all signs and symptoms that were severe at

admission would need to be absent or mild at the test of cure visit. If the result of any sign or symptom was unknown, the clinical response was non-evaluable.

To be considered a mycological cure the culture for any fungal species that was positive at admission would need to be negative at the test of cure visit. If the fungal culture was positive at the test of cure, the mycological response would be failure.

Secondary analyses included the effect of the subject's activity level, high or low, on therapeutic cure in the daytime group, clinical cure rate, mycological cure rate, individual vulvovaginal symptom relief, and time to vulvovaginal symptom relief. High activity level will include moderate or vigorous activity and low activity will include missing, inactive, and mild activity.

There were three analysis populations defined in the study protocol: a safety evaluable population, an intent-to-treat (ITT) population, and an efficacy evaluable population. The safety evaluable population included all subjects who used the study drug (either ovule or external cream) and who relayed safety information to the investigator. The intent-to-treat population consisted of all subjects who used the study drug, ovule or external cream. Subjects who discontinued or had missing outcome data were to be considered treatment failures for this population. The efficacy evaluable population included patients who did not have any major protocol violations. These violations include, but are not limited to, the following:

- did not use study drug
- were lost to follow-up
- had missing or negative culture for *Candida*
- had a test of cure visit prior to Day 21 or after Day 30
- had a missing clinical or mycological data at the test of cure visit, unless considered a failure on one of the two endpoints.

The efficacy evaluable population is considered the primary population by the sponsor; however, the division will consider the ITT of equal importance in the evaluation of the study.

Reviewer's comment: Though a modified intent-to-treat (MITT) population was not defined in the protocol, the medical reviewer requested that an analysis on this population be conducted as well. This population will be defined as all patients randomized who had a positive culture for Candida at admission. See Reviewer's Additional Analyses for the results of the analysis using this population.

Non-inferiority will be shown if the two-sided 95% confidence interval for the difference (daytime-bedtime) in rates of therapeutic cure excludes the non-inferiority margin of -15%. The sponsor calculated a necessary sample size of 260 patients per arm using an assumed 60% cure rate on both arms, 80% power, and a 35% non-evaluable rate.

Confidence intervals were calculated using the normal approximation to the binomial with a Hauck and Anderson continuity correction. The general form of the confidence interval is

$$P_D - P_B +/- (Z_{0.025} * \sigma + 100\ CC)$$

P_D, P_B are the observed daytime rate, bedtime rate
N_D, N_B are the sample sizes for the daytime group, the bedtime group.
Z is the value that defines an area of 0.025 in the upper tail of the standard normal distribution
σ is the standard deviation defined as square root of $[(P_D*(100-P_D)/N_D+(P_B*(100-P_B)/N_B)]$.
CC is the continuity correction defined as $(2* \min(N_D, N_B))^{-1}$

3.1.2 Enrollment and Withdrawal Information

A total of 573 subjects were enrolled into this study, 279 randomized to the daytime group and 294 to the bedtime group. Patients were enrolled by 53 investigators in the USA. Seven investigators enrolled at least 10 patients per arm. Four investigators did not enroll any subjects into the daytime group and four did not enroll any subjects into the bedtime group. Nine subjects randomized to the daytime group received the wrong Daily Diary card. All of these subjects took their medication according to the bedtime schedule. Five subjects randomized to the bedtime group received the wrong Daily Diary. Three of these patients took their medication according to the daytime schedule. The sponsor analyzed these subjects in the group corresponding to the actual time of study drug use.

Reviewer's comment: An analysis by original randomization schedule will be discussed in the Reviewer's Additional Analyses section.

The following table (Table 3) lists the number of patients included in each population and the number of patients excluded along with the reason for exclusion from a population.

Table 3: Inclusion/Exclusion of Patients from Study Populations

Population/Reason for Nonevaluability	Daytime (N=279)		Bedtime (N=294)	
Safety evaluable population	278	(99.6)	292	(99.3)
Did not take study drug or usage unknown	1	(0.4)	2	(0.7)
Intent-to-treat population	278	(99.6)	292	(99.3)
Did not take study drug or usage unknown	1	(0.4)	2	(0.7)
Efficacy evaluable population	149	(53.4)	163	(55.4)
Did not take study drug or usage unknown	1	(0.4)	2	(0.7)
Lost to follow-up	7	(2.5)	5	(1.7)
Negative or missing admission Candida culture	70	(25.1)	84	(28.6)
Positive/missing *C. trachomatis* or *N. gonorrhoeae*	1	(0.4)	3	(1.0)
Study drug incorrectly used	19	(6.8)	7	(2.4)
Used systemic antimicrobials or antifungals	12	(4.3)	12	(4.1)
Test of cure visit prior to day 21 or after day 30	9	(3.2)	2	(0.7)
Missing clinical or mycological data at test of cure visit	1	(0.4)	2	(0.7)
Failed exclusion or inclusion criteria	4	(1.4)	6	(2.0)
Developed other VV infection after admission	3	(1.1)	3	(1.0)
Pap smear with HPV, precan. lesion or carcinoma in-situ	3	(1.1)	5	(1.7)

Source: Table 3 from Sponsor's study report page 42

Only 3 patients were excluded from the ITT and Safety evaluable populations across the two treatment arms. Almost 50% of randomized patients were excluded from the efficacy evaluable population. The major reason for exclusion from the efficacy evaluable population was negative

or missing admission Candida culture. More patients were excluded from the daytime group than the bedtime group due to study drug used incorrectly and due to test of cure visit prior to day 21 or after day 30.

There was a total of 26 Daytime and 12 Bedtime who took the study drug but used it incorrectly. Of the 26 patients in the Daytime group 4 were also lost to follow-up and 3 had negative or missing culture. Of the 12 in the Bedtime group 1 was also lost to follow-up and 4 had missing or negative culture. Of the 19 and 7 patients excluded from the efficacy evaluable population due to drug used incorrectly, there were 9 cures and 10 failures on the Daytime arm and 4 cures and 3 failures on the Bedtime arm.

Note that seven subjects in each group were included in the efficacy evaluable population with a test of cure visit occurring outside the defined window of 21-30, but within a window of +/- 10% of the 21 to 30 day window. The sponsor did not state whether this change was made prior to unblinding the study. However, all of these patients were considered cures and the inclusion of these subjects into the efficacy evaluable population did not effect the overall conclusions of the study.

The rate of study discontinuation was slightly higher in the daytime group (11.1%) than the bedtime group (8.8%). The category with the largest difference was treatment failure/subject required additional VVC treatment (9 patients [3.2%] on the daytime arm and 2 patients [0.7%] on the bedtime arm). All of these patients were considered failures in the intent-to-treat analysis. Only 2 of the daytime patients and 1 of the bedtime patients were considered evaluable and all were considered failures. The table below contains the reasons for discontinuation by treatment as reported in the study report.

Table 4: Discontinuations

Reason for Discontinuation	**Daytime (N=279)**		**Bedtime (N=294)**	
Total discontinued	31	(11.1)	26	(8.8)
Subject request	2	(0.7)	1	(0.3)
Treatment failure/subject required additional VVC treatment	9	(3.2)	2	(0.7)
Adverse event	3	(1.1)	7	(2.4)
Lost to follow-up	8	(2.9)	6	(2.0)
Admission results	0	(0.0)	1	(0.3)
Other	9	(3.2)	9	(3.1)

Source: Table 4 from Sponsor's study report page 43

Reviewer's comment: The sponsor states that the order of reasons for discontinuation as listed in the table is the hierarchical order used to determine the primary reason. However, based on the data set, the actual hierarchical order used to create the table was 1) adverse event, 2) treatment failure, and 3) subject request, followed by the others. Using the sponsor's stated hierarchical order there are 4 (1.4%) discontinuation due to subject request for daytime and 1 (0.3%) for bedtime, 8 (2.9%) due to treatment failure for daytime and 6 (2%) for bedtime, and 2 (.7%) due to adverse event for daytime and 3 (1%) for bedtime.

3.1.3 Demographics and Baseline Variables

Demographics and baseline characteristics were generally comparable between the two treatment arms. All patients were female. Patients were on average 36 years old (range 16 to 84 years). Sixty-eight percent of randomized patients were Caucasian, 21% were Black, and 9% were Hispanic. Thirty-six percent had mild severity of disease, 56% had moderate severity and 8% severe. Additional signs and symptoms were also similar between treatments. The vast majority (91%) of fungal species at baseline in the evaluable population was *Candida albicans*. *Candida glabrata* was the next most common fungal species (8.0%).

3.1.4 Sponsor's Efficacy Results

Primary Efficacy Results

The primary endpoint is therapeutic cure analyzed using both the efficacy evaluable and the intent-to-treat patient populations. Therapeutic cure is made up of both clinical and microbiological response. The following two tables contain the sponsor's results for these three endpoints in the two populations. All of these analyses show non-inferiority, using a non-inferiority margin of 15% as defined in the protocol, since all confidence intervals exclude -15%.

Table 5: Sponsor's Primary Analysis on the Efficacy Evaluable Population

Response/Group	Daytime Monistat 1 n/N	(%)	Bedtime Monistat 1 n/N	(%)	95% Confidence Interval*
Therapeutic cure rates	**86/149**	**(57.7)**	**83/163**	**(50.9)**	**[-4.6, 18.2]**
Mycological cure rates	105/149	(70.5)	104/163	(63.8)	[-4.1, 17.4]
Clinical cure rates	111/149	(74.5)	120/163	(73.6)	[-9.2, 10.9]

* 95% confidence intervals calculated as Daytime – Bedtime
Source: Sponsor's table 8.1

Table 6: Sponsor's Primary Analysis on the Intent-to-treat Population

Response/Group	Daytime Monistat 1 n/N	(%)	Bedtime Monistat 1 n/N	(%)	95% Confidence Interval*
Therapeutic cure rates	**121/278**	**(43.5)**	**103/292**	**(35.3)**	**[0.1, 16.4]**
Mycological cure rates	141/278	(50.7)	130/292	(44.5)	[-2.2, 14.6]
Clinical cure rates	195/278	(70.1)	196/292	(67.1)	[-4.8, 10.8]

* 95% confidence intervals calculated as Daytime – Bedtime
Source: Sponsor's table 8.2

Cross tabulations of microbiologic and clinical responses in efficacy evaluable population

The following table compares the microbiologic response with the clinical response for the evaluable for efficacy population. For example, 86 of 149 (57.7%) patients in the daytime group

were both clinical and microbiologic cures, while 83 of 163 (50.9%) patients in the bedtime group were both clinical and microbiologic cures.

Reviewer's comment: The Kappa Statistic is also reported in this table. The Kappa Statistic, which can range from -1 to 1, is a quantitative measure of reproducibility of drug benefit measured with two nominal endpoints. A Kappa value of 1 means perfect positive correlation, while a Kappa of -1 means perfect negative correlation. In this example, its use is to evaluate the correlation between clinical and microbiological response. Both values of Kappa, for daytime and bedtime administration, show positive Kappa values. This shows positive correlation. Similar values of Kappa were seen with the intent-to-treat population.

Table 7: Microbiologic and Clinical Response Correlation for the Efficacy Evaluable Population

Clinical Response	Micro Response Cure	Failure	Missing/not interpretable	Total	Kappa Statistic
Daytime Monistat 1					
Cure	86	25	0	111	
Failure	19	16	1	36	
Non-Evaluable	0	0	2	2	
Total	105	41	3	149	0.219 (SE 0.088)
Bedtime Monistat 1					
Cure	83	37	0	120	
Failure	21	20	0	41	
Non-Evaluable	0	0	2	2	
Total	104	57	2	163	0.159 (SE 0.079)

Source: Sponsor's table 9; Kappa Statistic calculated by reviewer

Therapeutic cure rates by activity levels

The sponsor grouped activity levels into Low (None and Mild) and High (Moderate and Vigorous) for the daytime group. The sponsor then compared the Low Activity Level group with the High Activity Level group. No statistically significant differences were found between these two groups. However, it appears that the high activity level has lower microbiological cure rates but higher clinical cure rates than the low activity level.

Table 8: Sponsor's analysis by activity level in the daytime group (Efficacy Evaluable)

Response/Group	Low Activity Level n/N	(%)	High Activity Level n/N	(%)	Fisher's Exact Test	Difference [95% confidence interval]*
Efficacy Evaluable						
Therapeutic cure rates	26/43	(60.5)	59/105	(56.2)	0.7154	4.3% [-14.3, 22.9]
Mycological cure rates	35/43	(81.4)	69/105	(65.7)	0.0746	15.7% [-0.2, 31.6]
Clinical cure rates	30/43	(69.8)	80/105	(76.2)	0.4156	-6.4% [-23.5, 10.7]
Intent to Treat						
Therapeutic cure rates	39/80	(48.8)	80/186	(43.0)	0.4212	5.7% [-7.9, 19.4]
Mycological cure rates	48/80	(60.0)	91/186	(48.9)	0.1091	11.1% [-2.5, 24.6]
Clinical cure rates	53/80	(66.3)	140/186	(75.3)	0.1368	-9.0% [-21.7, 3.7]

* Calculated as Low - High

Source: Sponsor's tables 10.1 and 10.2; Confidence intervals provided by reviewer

Reviewer's comment: Note that lack of statistical significance does not imply that there is not a difference in efficacy between low and high activity levels. Ninety-five percent confidence intervals are also given to help understand the variability of the observed difference. Also, note that the activity level groups are based on post-randomization information. Therefore inclusion into these groups may not be independent of outcome.

Reviewer's comment: An analysis by actual activity level for both efficacy evaluable and intent-to-treat patient populations will be discussed in the Reviewer's Additional Analyses section.

Time to symptom relief

The sponsor evaluated time to vulvovaginal symptom relief, based on subjects' estimated time to initial relief. The sponsor's results show that for all three symptoms, itching, burning, and irritation, the time to symptom relief was very similar between the two arms. These results for the efficacy evaluable population are reported in the table below. None of these differences reached statistical significance.

Table 9: Time to Initial Relief (Efficacy Evaluable)

	Daytime Monistat 1		Bedtime Monistat 1	
Symptom/Group	Median hours	n*	Median hours	n*
Itching	36	133	36	143
Burning	24	102	36	113
Irritation	48	136	42	146
All three	72	94	72	104

* n = number reporting symptom at admission

Source: from Sponsor's tables 11, 12, 13, 14.

Microbiology

The number of evaluable subjects with a positive culture at the return visit was 99, down from 312 at admission. The majority of these subjects had *C. albicans*. In the intent-to-treat population, the number of subjects with a positive culture at the return visit was 130, down from 410 at admission. The results were similar between the two groups. The following table reports the culture results at the return visit for the intent-to-treat population.

Table 10: Culture Results at Return Visit for Intent-to-treat Population

	Daytime N=278		Bedtime N=292	
	n	(%)	N	(%)
Culture Positive	54	(19.4%)	76	(26.0%)
Candida albicans	41	(14.7%)	61	(20.9%)
Candida glabrata	8	(2.9%)	11	(3.8%)
Other *Candida*	5	(1.8%)	4	(1.4%)
Culture Negative	196	(70.5%)	198	(67.8%)
Culture Missing	28	(10.1%)	18	(6.2%)

Source: Reviewer's analysis from Key and Micro data sets

For a more detailed discussion of the culture results please see the microbiologist's review.

3.1.5 Reviewer's Additional Analyses

Analyses based on original randomization

Nine subjects randomized to the daytime group (50106, 53508, 54707, 56208, 56407, 56408, 57506, 57507, and 66109) received the wrong Daily Diary card and took their medication according to the bedtime schedule. Three subjects randomized to the bedtime group (60206, 60208, and 64707) received the wrong Daily Diary and took their medication according to the daytime schedule. The sponsor analyzed these subjects in the group corresponding to the actual time of study drug use. In order to maintain the randomization of this study, a more appropriate way to analyze these patients would be as they were randomized rather than by the timing of their dose. When these subjects are analyzed by the original randomization schedule the following results are obtained (Table 11). Non-inferiority is still maintained. However, the borderline significance in the sponsor's intent-to-treat analysis is no longer seen. Note that the remaining analyses will be based on the sponsor's data sets.

Table 11: Primary Analysis by Original Randomization Schedule

Therapeutic Cure Rate	Daytime Monistat 1 n/N	(%)	Bedtime Monistat 1 n/N	(%)	95% Confidence Interval*
Intent to treat	119/284	(41.9)	105/286	(36.7)	[-3.0, 13.4]
Efficacy Evaluable	86/155	(55.5)	83/157	(52.9)	[-8.8, 14.0]

* 95% confidence intervals calculated as Daytime – Bedtime

Source: Reviewer's analysis

Analyses of activity level

Subjects' activity levels were to be classified as mild, moderate, or vigorous with classification based on majority of time spent at activity level for each of the 4 hours following administration. The protocol stated that 20% should have vigorous activity within the first 4 hours following treatment administration and 80% should have moderate to vigorous activity. Diary information was collected on 267 (96%) of daytime patients. The actual levels of activity obtained for the daytime group were 19.1% obtaining vigorous activity, and 69.7% obtaining moderate or vigorous. Note that subjects reported their majority activity level per hour after treatment and not their specific activity conducted or amount of time doing that activity.

In the sponsor's analysis, the sponsor reclassified patients into low and high with high being moderate or vigorous and low being all others. The following tables report efficacy by actual maximum activity level obtained within the first four hours after administration. Response rates for all activity levels are similar to those seen with the bedtime group. However, note that these subgroups are based on post-randomization information. Therefore inclusion into these groups may not be independent of outcome. For example, it could be the case that patients in the vigorous group felt well, and then chose to undertake a vigorous activity.

Table 12: Response by Activity Level for Efficacy Evaluable Population

	Therapeutic Cure rates		Micro Cure Rates		Clinical Cure rates	
Group/response	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Daytime by activity level						
Missing	1/1	(100)	1/1	(100)	1/1	(100)
Inactive	4/4	(100)	4/4	(100)	4/4	(100)
Mild	22/39	(56.4)	31/39	(79.5)	26/39	(66.7)
Moderate	38/75	(50.7)	48/75	(64.0)	54/75	(72.0)
Vigorous	21/30	(70.0)	21/30	(70.0)	26/30	(86.7)
Bedtime	83/163	(50.9)	104/163	(63.8)	120/163	(73.6)

Source: Reviewer's analysis

Table 13: Response by Activity Level for Intent-to-treat Population

	Therapeutic Cure rates		Micro Cure Rates		Clinical Cure rates	
Group/response	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Daytime by activity level						
Missing	2/12	(16.7)	2/12	(16.7)	2/12	(16.7)
Inactive	5/7	(71.4)	5/7	(71.4)	5/7	(71.4)
Mild	34/73	(46.6)	43/73	(58.9)	48/73	(65.8)
Moderate	51/135	(37.8)	62/135	(45.9)	97/135	(71.9)
Vigorous	29/51	(56.9)	29/51	(56.9)	43/51	(84.3)
Bedtime	103/292	(35.3)	130/292	(44.5)	196/292	(67.1)

Source: Reviewer's analysis

Use of intravaginal products

The draft guidance for developing antimicrobial drugs for treatment of vulvovaginal candidiasis states that patients should refrain from using intravaginal products because the use of such products may preclude accurate assessment of the study drug's efficacy as well as safety and that if a patient used these products (douche, N- 9 products, condoms, tampons) during the first 7 days this patient should be considered unevaluable (excluded from the evaluable population). However, in the analysis of this protocol these patients were not necessarily considered unevaluable.

The study report and protocol state that subjects were to refrain from use of any intravaginal product for the duration of the study. Subjects were also asked specifically not to use tampons for at least 7 days after study drug use. The case report form asks if the patient used tampons within 7 days of administration of study drug and if any vulvovaginal therapeutics, douche, or feminine spray were used at any time during the study.

Regarding the use of tampons within 7 days of administration of study drug, 4 subjects were found, 2 in the daytime group and 2 in the bedtime group. Of these, one daytime subject and one bedtime subject were considered evaluable. The daytime subject was considered a failure and the bedtime subject was considered a cure. Changing these two subjects to non-evaluable would not change the overall study results.

Regarding the use of other vulvovaginal products, using the data set RXHX containing pertinent history, two evaluable daytime patients (1 failure) and four evaluable bedtime patients (2 failures) were found to have used douche or feminine spray, tampons, or a vulvovaginal therapeutic. However, it does not state whether use was within 7 days of drug administration. Using the diary data sets (Diary_1 and Diary_2) additional patients were found to have used vulvovaginal products, 6 evaluable daytime patients (4 cures) and 8 evaluable bedtime patients (4 cures). These products included spermacide, feminine wash, sanitary pad, KY jelly, and antibacterial wipe. Again it does not state whether use was within 7 days of drug administration. Note that two subjects were found using both datasets.

A sensitivity analysis was conducted by removing all of these evaluable patients (7 daytime (5 cures), 11 bedtime (5 cures)) from the primary evaluable analysis. The results give a daytime therapeutic cure rate of 81/142 (57%) and a bedtime therapeutic cure rate of 78/152 (51%). The overall conclusions of this study do not change.

By center analysis

There were a large number of centers, 53, making an analysis by center difficult. To make sure that the few large centers were not overly influencing the results the following four analyses of therapeutic cure in the intent-to-treat population were conducted by center size:

- include only centers with 40 or more subjects (3 centers)
- include only centers with 20 or more subjects (7 centers)
- include only centers with 10 or fewer subjects (34 centers)
- include only centers with fewer than 20 subjects (46 centers)

The analysis looking at only the 3 centers with 40 or more subjects showed the daytime therapeutic cure of 38/69 (55.1%) versus 33/70 (47.1) for bedtime. Including centers with 20 or more gives a daytime rate of 60/114 (52.6%) versus a bedtime rate of 52/116 (44.8%). Looking at an analysis of only centers with 10 or fewer patients gives the following results, daytime therapeutic cure of 33/85 (38.8%) versus bedtime therapeutic cure 24/93 (25.8%). Results with centers of size 20 or fewer gives 61/164 (37.2) for daytime and 51/176 (29.0) for bedtime Overall cure rates are lower when looking at only the small centers, however, the treatment effect are approximately the same.

Modified Intent-to-treat Analysis Population

As mentioned in section 3.1.1, though a modified intent-to-treat (MITT) population was not defined in the protocol, the medical reviewer requested that an analysis on this population be conducted as well. This population is defined as all intent-to-treat patients who had a positive culture for Candida at admission. The following table gives the results of this analysis. The overall results remain the same.

Table 14: Analysis on the Modified Intent-to-treat Population

Response/Group	Daytime Monistat 1 n/N	(%)	Bedtime Monistat 1 n/N	(%)	95% Confidence Interval*
Therapeutic cure rates	**121/204**	**(59.3)**	**103/206**	**(50.0)**	**[-0.5, 19.2]**
Mycological cure rates	141/204	(69.1)	130/206	(63.1)	[-3.4, 15.4]
Clinical cure rates	151/204	(74.0)	147/206	(71.4)	[-6.2, 11.5]

* 95% confidence intervals calculated as Daytime – Bedtime
Source: Reviewer's analysis

3.2 Evaluation of Safety

Treatment emergent adverse event was defined as any unfavorable and unintended sign, symptom, or disease associated with the use of study drug, regardless of relationship to study drug. Serious adverse event was defined as any event that was fatal or life threatening, was permanently disabling, required or prolonged hospitalization or was a congenital anomaly or birth defect.

Similar number of subjects reported adverse events, 143 (51.4%) on the daytime arm and 140 (47.9%) on the bedtime arm. The majority of these events were listed as reproductive system and breast disorders (26.6% of daytime and 26.4% of bedtime). The majority of these were vulvovaginal discomfort.

The majority of adverse events were considered mild or moderate. There were 33 (11.9%) adverse events in daytime group that were considered severe and 37 (12.7%) in the bedtime group. Seventeen in the daytime group and 16 in the bedtime group were vulvovaginal discomfort.

There were 3 serious adverse events reported by 2 subjects, one in the bedtime group and one in the daytime group. The subject in the bedtime group experienced a worsening of undifferentiated schizophrenia on day 20. The subject in the daytime group experienced nausea and vomiting NOS on day 3 and was hospitalized. A urine toxicology screen revealed current use of cocaine and cannabinoid. These events were considered unlikely related to study drug.

For a more detailed discussion of the safety of this study please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All patients enrolled in this study were female.

The majority of randomized patients were Caucasian (68%) with 21% black, and 9% Hispanic. Table 15 below gives the therapeutic cures rates by race. The 95% confidence intervals for black patients are completely above 0, implying that the Daytime group has a higher cure rate than the Bedtime group. Note that these confidence intervals are not adjusted for multiple comparisons. A logistic regression with race and treatment did not find a significant interaction in the intent-to-treat population, but did find a significant interaction in the evaluable population. This interaction is mainly due to the significant results seen with black patients. Note that these patients have a higher therapeutic cure rate in the Daytime group, the test group, and therefore is not a concern.

Table 15: Therapeutic Cure by Race

Therapeutic cure rates /Group	**Daytime Monistat 1 n/N**	**(%)**	**Bedtime Monistat 1 n/N**	**(%)**	**95% Confidence Interval***
Intent to Treat					
Caucasian	84/189	(44.4)	72/197	(36.6)	[-2.1, 17.9]
Black	28/61	(45.9)	16/60	(26.7)	[1.6, 36.8]
Hispanic	9/26	(34.6)	13/28	(46.4)	[-39.7, 16.1]
Evaluable					
Caucasian	60/106	(56.6)	60/115	(52.2)	[-9.2, 18.0]
Black	21/30	(70.0)	14/34	(41.2)	[3.9, 53.8]
Hispanic	5/12	(41.7)	8/10	(80.0)	[-72.2, 4.8]**

* 95% confidence intervals calculated as Daytime – Bedtime
** Exact confidence interval
Source: Reviewer's analysis
Note 9 subjects (7 Asian and 2 other) in the intent-to-treat population and 5 subjects (3 Asian and 2 other) in the evaluable population were not included.

Patients were on average 36 years old (range 16 to 84 years). No significant interaction between age and treatment was found in a logistic regression model. The following table shows therapeutic cures for patients 16-64 and > 64 and by age quartiles (< 25, 25-34, 35-44, > 44 years). However, there were very few patients greater than or equal to 65 years old (6 on daytime and 10 on bedtime). Daytime patients between the ages 35 and 44 showed a higher therapeutic cure rate than bedtime patients.

Table 16: Therapeutic Cure by Age

Therapeutic cure rates /Group	Daytime Monistat 1 n/N	(%)	Bedtime Monistat 1 n/N	(%)	95% Confidence Interval*
Intent to Treat					
18-64	119/272	(43.8)	102/282	(36.2)	[-0.7, 15.9]
>64	2/6	(33.3)	1/10	(10.0)	[-19.1, 62.4]**
<25	34/65	(52.3)	35/80	(43.8)	[-8.5, 25.6]
25-34	31/73	(42.5)	33/75	(44.0)	[-18.2, 15.1]
35-44	32/72	(44.4)	14/65	(21.5)	[6.9, 38.9]
>44	24/68	(35.3)	21/72	(29.2)	[-10.1, 22.3]
Evaluable					
18-64	84/146	(57.5)	82/158	(51.9)	[-9.2, 18.0]
>64	2/3	(66.7)	1/5	(20.0)	[-26.2, 88.8]**
<25	23/39	(59.0)	26/51	(51.0)	[-13.9, 29.9]
25-34	23/40	(57.5)	28/40	(70.0)	[-34.6, 9.6]
35-44	23/40	(57.5)	11/29	(37.9)	[-5.5, 44.7]
>44	17/30	(56.7)	18/43	(41.9)	[-9.9, 39.5]

* 95% confidence intervals calculated as Daytime – Bedtime
** Exact confidence interval
Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

There was not a significant interaction by overall severity at admission. There were no additional subgroup analyses performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no major statistical issues in this NDA. The sponsor analyzed patients by how patients administered study drug, either daytime or bedtime administration, as opposed to by their randomization code. This reviewer did an analysis by randomization and the overall results remain the same.

This NDA contains only one phase III study to provide evidence on the validity of removing the words "at bedtime" regarding the administration of the product from the drug label.

5.2 Conclusions and Recommendations

Personal Products Company, the sponsor, conducted one phase III study to show that daytime administration of the Monistat Ovule as part of the Monistat 1 Combination Pack has similar efficacy to bedtime administration of the ovule, the currently approved administration time. Additionally they recorded activity level to ensure that moderate to vigorous activity within 4 hours of administration would not reduce the efficacy of the product.

The results of the phase III study showed that efficacy of the daytime administration is non-inferior to the bedtime administration, using a non-inferiority margin of 15%. Furthermore, efficacy does not seem to be reduced in those subjects obtaining moderate to vigorous activity within 4 hours of administration compared to those subjects administering the product at bedtime.

The results of the study support the change in labeling removing the words "at bedtime".

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/s/

Karen Higgins
9/3/04 04:48:37 PM
BIOMETRICS

Mohammad Huque
9/9/04 11:24:30 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

CLINICAL MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 21-308

REVIEWER : Kalavati Suvarna
CORRESPONDENCE DATE : 12-02-03
CDER RECEIPT DATE : 12-03-03
REVIEW ASSIGN DATE : 02-02-04
REVIEW COMPLETE DATE : 07-22-04

SPONSOR: Personal Products Company
Division of McNeil-PPC, Inc.
199 Grandview Road,
Skillman, NJ 08558.

SUBMISSION REVIEWED: SE2-009

DRUG CATEGORY: Anti-fungal

INDICATION: Treatment of vulvovaginal candidiasis

DOSAGE FORM: Vaginal ovule (1200 mg)

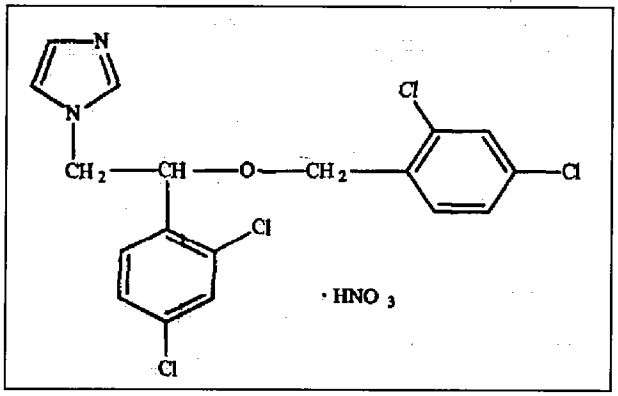
PRODUCT NAMES:

a. **PROPRIETARY:** MONISTAT® 1 Combination Pack

b. **NONPROPRIETARY:** Miconazole Nitrate

c. **CHEMICAL:** 1-[2,4-dichloro-b-{(2,4-dichlorobenzyl)oxy}phenethyl]imidazolemononitrate.

STRUCTURAL FORMULA:



Molecular weight: 479.15
Empirical Formula: $C_{18}H_{14}Cl_4N_2O.HNO_3$

SUPPORTING DOCUMENTS:

NDA 17-450, NDA 18-520, NDA 20-670, NDA 20-872, NDA 21-308, NDA 20-288, NDA 20-968, NDA 21-261, NDA 18-888, IND 37,522.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY:

Miconazole nitrate (1200 mg ovule plus 2% external cream) has been approved for the treatment of vulvovaginal candidiasis (VVC) as an OTC formulation. However, the product is labeled for bedtime use only. In a clinical study, the clinical and mycological outcome of miconazole nitrate (1200 mg ovule plus 2% external cream) administered at daytime was similar to that at bedtime. The VVC infection in a majority of patients was due to *C. albicans*. There were few patients with infections due to *Candida* species other than *C. albicans* (*C. krusei*, *C. parapsilosis,* and *C. tropicalis*).

The miconazole MICs against baseline isolates from patients failing treatment were in the same range as that for isolates from patients with a successful clinical outcome. Please note that the breakpoints for miconazole have not been established.

Some isolates with reduced susceptibility to miconazole also showed reduced susceptibility to other azoles (clotrimazole, terconazole, fluconazole and/or butaconazole), suggesting cross-resistance between azoles.

The product is for OTC use and contains only a consumer package insert. No microbiology information is described in the consumer package insert.

2. INTRODUCTION AND BACKGROUND:

Miconazole nitrate (1200 mg ovule plus 2% external cream) has been approved for the treatment of vulvovaginal candidiasis (VVC) as an OTC formulation since June 2001(NDA 21-308). The product is labeled for bedtime use. In this submission, the sponsor is seeking approval to change the label instructions for miconazole nitrate (1200 mg ovule plus 2% external cream) to allow for daytime use of the drug in addition to current bedtime administration based on data from a large multi-center phase III clinical trial.

3. PRECLINICAL MICROBIOLOGY:

The activity of miconazole against *Candida* sp. is well known. The minimum inhibitory concentration (MIC) values for miconazole against most fungi ranged between 0.01-100 μg/ml. No additional preclinical microbiology studies were included in this submission.

4. CLINICAL MICROBIOLOGY:

The sponsor conducted a single multi-center, randomized, parallel-group, investigator-blinded, phase III study (#CA-P-2343) to determine the safety and efficacy of a single vaginal dose of miconazole nitrate (1200 mg ovule) in combination with 2% external cream administered at daytime (anytime during the day before 7 pm) versus at bedtime (2 hours before sleeping). A total of 573 female subjects ≥ 12 years with VVC were enrolled. Patients with cervical neoplasia or vulvovaginal/genital infections such as bacterial vaginosis, trichomonal vaginitis, infections due to *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, herpes simplex, or human papilloma

virus, were excluded. Patients with known HIV seropositivity and those receiving other antifungal or antimicrobial therapies or having allergic reactions to imidazole class of drugs were also excluded. For additional details on the study design, please see Medical Officer's review.

The primary efficacy endpoint was therapeutic cure (clinical and microbiological), at 21-30 days after initiation of treatment. Microbiological cure was based on the culture for *Candida* species being negative. The secondary efficacy determinants were (a) clinical cure rate, (b) microbiological cure rate, and (c) time required for complete relief from clinical symptoms.

The subjects were evaluated for clinical and microbiologic outcomes, at baseline, interim visit (if therapy was discontinued), and 21-30 days after initiation of treatment.

For fungal culture, vaginal swabs were shipped in Amies charcoal transport medium. The fungal culture was performed by plating on Blood agar, Sabouraud's (Emmon's) agar, and Sabouraud's dextrose agar with chloramphenicol and incubating the cultures at 34 - 36°C for 5 days. Wet mount and the [redacted] were used to identify the yeast species. In the event that the [redacted] system failed, the [redacted] system was used. Identification of *Candida albicans* based on chlamydospore production using the cornmeal agar test was carried out if required.

Of the 573 patients, 308 (daytime, n = 147; bedtime, n = 161) met the inclusion and exclusion criteria and had a test-of-cure evaluation. The clinical and mycological outcomes of patients stratified by their baseline pathogen are shown in Table 1. The majority of baseline infections were due to *C. albicans* (daytime arm, n = 135; bedtime arm, n = 143). The percentage of patients with resolution of VVC symptoms and eradication of baseline *C. albicans* was similar in the two treatment arms (daytime = 62%; bedtime = 55%). Few patients were infected with *Candida* species other than *C. albicans*. The other *Candida* species included *C. glabrata* (daytime arm, n = 8; bedtime arm, n = 13), *C. krusei* (daytime arm, n = 2; bedtime arm, n = 1), *C. parapsilosis* (daytime arm, n = 2; bedtime arm, n = 1), *C. tropicalis* (daytime arm, n = 0; bedtime arm, n = 2), and *C. dubliniensis* (daytime arm, n = 0; bedtime arm, n = 1). Resolution of VVC symptoms and eradication of baseline yeasts was observed in 4 patients with *C. glabrata* (daytime arm, n = 1; bedtime arm, n = 3), 1 patient with *C. krusei* (daytime arm), and 1 patient with *C. parapsilosis* (bedtime arm).

Table 1: The clinical and mycological outcome of patients with VVC stratified by baseline pathogen.

Organism (number of patients)	Clinical and mycological cure	Clinical cure and mycological failure	Clinical failure and mycological cure	Clinical and mycological failure	Clinical failure and mycology not done
Daytime Monistat ovule (1200 mg) + 2% external cream					
C. albicans (n = 135)	84 (62%)	16 (12%)	19 (14%)	15 (11%)[a]	1 (1%)
C. glabrata (n = 8)	1	5	1	1	0
C. krusei (n = 2)	1	1	0	1	0
C. parapsilosis (n = 2)	0	0	2	0	0
Bedtime Monistat ovule (1200 mg) + 2% external cream					
C. albicans (n = 143)	79 (55%)[b]	32 (22%)	19 (13%)[a]	13 (9%)[a]	0
C. glabrata (n = 13)	3	4[a]	1	5	0
C. krusei (n = 1)	0	0	0	1	0
C. parapsilosis (n = 1)	1	0	0	0	0
C. tropicalis (n = 2)	0	0	1	1	0
C. dubliniensis (n = 1)	0	1	0	0	0

[a]1 patient had mixed infection due to *C. albicans* and *C. glabrata*
[b]2 patient had mixed infections (*C. albicans* + *C. glabrata*, n = 1; *C. albicans* + *C. krusei*, n =1).

Seven patients (5 in the daytime arm and 2 in the bedtime arm) had new infections at the test-of-cure visit due to a pathogen different from that identified at baseline (Table 2)

Table 2: Patients with new infections in study CA-P-2343.

Patient ID	Treatment arm	Baseline pathogen	New pathogen at test of cure visit
52509	DAYTIME	*C. glabrata*	*C. tropicalis*
61506	DAYTIME	*C. krusei*	*C. parapsilosis*
63406	DAYTIME	*C. albicans*	*C. lusitaniae*
68607	DAYTIME	*C. glabrata*	*C. albicans*
69606	DAYTIME	*C. albicans*	*C. glabrata*
55707	BEDTIME	*C. albicans*	*C. parapsilosis*
57107	BEDTIME	*C. albicans*	*C. glabrata*

Susceptibility testing of isolates collected at baseline and at 21-30 days after initiation of treatment was performed using the NCCLS microbroth dilution method (M27A). Please note that breakpoints for miconazole have not been established. The baseline miconazole MIC values of *C. albicans* and *C. glabrata* isolates from patients who showed resolution of VVC symptoms and those who failed clinically overlapped (Table 3). The number of patients with *Candida* species other than *C. albicans* (*C. krusei*, *C. parapsilosis*, and *C. tropicalis*) were too small to correlate the baseline miconazole MIC values with clinical outcome. Although changes (increase or decrease) in MIC were noted in pre-treatment and post-treatment isolates, these changes did not correlate with clinical outcome.

Table 3. Baseline miconazole MIC range for the different isolates and correlation with clinical outcome.

Pathogen	Miconazole MIC range in µg/ml of isolates from patients with clinical cure (number of isolates)	Miconazole MIC range in µg/ml of isolates from patients with clinical failure (number of isolates)
C. albicans	≤0.06 – 32.0 (214)	≤0.06 – 32.0 (64)
C. glabrata	≤0.06 – 32.0 (13)	1.0 - 32.0 (8)
C. krusei	≤0.06 – 8.0 (2)	16 (1)
C. parapsilosis	0.12 (1)	4 - 8 (2)
C. tropicalis	- (0)	16 (2)

Baseline miconazole MICs were compared with baseline MICs for fluconazole, clotrimazole, terconazole, and butaconazole against all isolates. The results in Table 4 show that some isolates with high miconazole MIC value (16-32 µg/ml) also showed increase in MIC values for azoles other than miconazole (clotrimazole, terconazole, fluconazole, and/or butaconazole), suggesting cross-resistance between azoles.

Table 4: The MIC ranges for clotrimazole, terconazole, fluconazole and butaconazole stratified by baseline miconazole MIC values.

Miconazole MIC in µg/ml (number of isolates)	**Clotrimazole MIC range in µg/ml**	**Terconazole MIC range in µg/ml**	**Fluconazole MIC range in µg/ml**	**Butaconazole MIC range in µg/ml**
0.06 (n = 235)	≤0.06 – 0.25	≤0.06 – 0.12	≤0.06 – 16.0	≤0.06
0.12 (n = 19)	≤0.06 – 0.5	≤0.06 – 0.25	0.25 – 4.0	≤0.06
0.25 (n = 8)	0.12 – 0.5	≤0.06 – 1.0	0.25 – 1.0	≤0.06
0.5 (n = 8)	0.25 – 4.0	≤0.06 – 1.0	0.25 – 16.0	≤0.06 – 0.25
1.0 (n = 4)	0.5 – 8.0	≤0.06 – 1.0	1.0 – 16.0	≤0.06 – 0.12
4.0 (n = 4)	0.12 – 16.0	≤0.06 – 8.0	0.5 – 8.0	≤0.06 – 0.5
8.0 (n = 12)	0.5 – 16.0	0.25 – 4.0	1.0 – 64.0[a]	0.12 – 4.0
16 (n = 12)	1.0 – 128.0	0.12 – 128.0	0.5 – 128.0[b]	0.06 – 128.0
32 (n = 10)	2.0 – 16.0	2.0 – 32.0	16.0 – 128.0[c]	0.5 – 32.0

[a] 4 isolates had fluconazole MIC = 64 µg/ml
[b] 7 isolates had fluconazole MIC ≥ 64 µg/ml
[c] 6 isolates had fluconazole MIC ≥ 64 µg/ml

5. LABEL:

The product is for OTC use and contains only a consumer package insert. There are no microbiology issues with the consumer package insert.

6. CONCLUSIONS:

Miconazole nitrate (1200 mg ovule plus 2% external cream) has been approved for the treatment of vulvovaginal candidiasis (VVC) for bedtime use. The sponsor conducted a phase III study to evaluate the safety and efficacy of miconazole nitrate (1200 mg ovule plus 2% external cream) when administered at bedtime versus daytime. The results from this study show that the clinical and mycological outcome of miconazole nitrate (1200 mg ovule plus 2% external cream) administered at daytime was similar to that at bedtime. The VVC infection in a majority of patients was due to *C. albicans*. There were few patients with infections due to *Candida* species other than *C. albicans* (*C. krusei*, *C. parapsilosis,* and *C. tropicalis*). New infections due to a *Candida* species other than the one observed at baseline was observed in 7 patients (daytime arm = 5; bedtime arm = 2).

There was no correlation between miconazole MIC and clinical outcome. Please note that the breakpoints for miconazole have not been established.

Some isolates with reduced susceptibility to miconazole also showed reduced susceptibility to azoles other than miconazole (clotrimazole, terconazole, fluconazole and/or butaconazole), suggesting cross-resistance between azoles.

7. RECOMMENDATIONS:

This NDA is recommended for approval with respect to Microbiology.

Kalavati Suvarna
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/Deputy Dir _____Signature _____Date
HFD-590/Micro TL _____Signature _____Date
CC:
HFD-590/Original IND
HFD-590/Division File
HFD-590/MO
HFD-590/Pharm
HFD-590/Chem
HFD-590/Review Micro
HFD-590/CSO/HomonnayA

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/s/

Kalavati Suvarna
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MICROBIOLOGIST

Shukal Bala
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MICROBIOLOGIST

Steve Hundley
8/1/04 12:43:28 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA #: 21-308 SUPPL #: 009

Trade Name: Monistat 1 Combination Pack Generic Name:

Applicant Name: Personal Products Company HFD #: HFD-560

Approval Date: October 1, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /**X**/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE-2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /**X**/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /__X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	**20-968**	**18-520**	**17-494**
NDA#	**21-261**	**20-288**	**18-888**
NDA#	**17-450**	**20-827**	**20-968**
	20-670		

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /__X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO **/ X /**

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Clinical Study Protocol Number: CA-P-2343

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /**X**/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /**X**/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

#CA-P-2343 _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the

investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # **37,522** YES **/ X /**	NO /___/ Explain: _____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO **/ X /**

If yes, explain: _____

_____

Signature Date:
Title: Regulatory Project Manager HFD-560

Signature of Office/Division Director Date:

Form OGD-011347 Revised 05/10/2004

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/s/

Charles Ganley
10/1/04 11:14:50 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-308 **Supplement Type (e.g. SE5):** SE2 **Supplement Number:** 009

Stamp Date: December 3, 2003 **Action Date:** October 1, 2004

HFD- 560 **Trade and generic names/dosage form:** Monistat 1 Combination Pack, miconazole nitrate 1200 mg vaginal insert and 2% cream

Applicant: Personal Products Company **Therapeutic Class:**

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of vulvovaginal candidiasis and relief of external vulvar irritaiton

Is there a full waiver for this indication (check one)?

- ✓ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ✓ **Disease/condition does not exist in children prior to menarchy**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ✓ **Other: Per original switch application: The adult clinical data can be extrapolated to postmenarchal girls**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA 21-308
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Leah Cutter
9/29/04 03:02:01 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-308	Efficacy Supplement Type SE-2	Supplement Number 009	
Drug: Monistat 1 Combination Pack (miconazole nitrate)		Applicant: Personal Products Company	
RPM: Leah Cutter, Ph.D.		HFD-560	Phone # 301-827-2248

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 3, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4646
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified (X) N/A 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No,**" continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	✓
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM Filing Review 20-Jan-04 MO Fileability Checklist 13-Jan-04

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X)Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	OTC Labeling Review 29-Jul-04, 27-Aug-04,22-Sep-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	OTC Labeling Review 29-Jul-04, 27-Aug-04,22-Sep-04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	24-Jun-02
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	28-Sep-04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	01-Aug-04
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	29-Sep-04
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	09-Sep-04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Leah Cutter
9/30/04 10:46:19 AM
CSO

45-DAY MEETING
Fileability Checklist
NDA __21-308____ (S-009)
— *CLINICAL* —

Based on your initial overview of the NDA submission:	Yes	No	N/A
1. On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	X	☐	☐
2. Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	X	☐	☐
3. On its face, is the clinical section of the NDA legible so that a substantive review can begin?	X	☐	☐
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X	☐	☐
5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X	☐	☐
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X	☐	☐
7. Are all data sets for pivotal efficacy studies complete for all indications requested?	X	☐	☐
8. Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X	☐	☐
9. Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's Guidance for Industry – Archiving Submissions for Electronic Format — NDAs?	X	☐	☐
10. Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	☐	☐	X

Based on your initial overview of the NDA submission:	Yes	No	N/A
11. Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division?	☐	☐	X
12. If CRFs were submitted electronically, are they consistent with CDER's Guidance for Industry - Archiving Submissions for Electronic Format — NDAs?	X	☐	☐
13. Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X	☐	☐
14. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	☐	X	☐
15. Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package?	X	☐	☐
16. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	☐	☐	X

17. From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) ____Yes_____

18. If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

_____
Clinical Reviewer (sign & date)

_____
Medical Team Leader (sign & date)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joette Meyer
1/9/04 03:46:29 PM
MEDICAL OFFICER

Rigoberto Roca
1/13/04 05:56:52 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-308 Supplement # 009 SE1 (SE2) SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Monistat 1 Combination Pack
Generic Name: Miconazole Nitrate
Strengths: 1200 mg vaginal insert and 2% external cream

Applicant: Personal Products Company

Date of Application: December 2, 2003
Date of Receipt: December 3, 2003
Date clock started after UN:
Date of Filing Meeting: January 12, 2004
Filing Date: February 1, 2004
Action Goal Date (optional): User Fee Goal Date: October 3, 2004

Indication(s) requested: Treatment of vulvovaginal candidiasis and relief of external vulvar irritation

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) __X__ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S __X__ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) OTC

User Fee Status: Paid __X__ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: (YES) NO
User Fee ID # 4646
Clinical data? YES __X__ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES (NO)

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES (NO)

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES (NO)

Is the application affected by the Application Integrity Policy (AIP)? YES (NO)
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? (YES) NO
- Was form 356h included with an authorized signature? (YES) NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? (YES) NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A (YES) NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Item 12: Case Report Forms

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? (N/A) YES NO

- Is it an electronic CTD? (N/A) YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted on form FDA 3542a? (YES) NO

- Exclusivity requested? YES, _____years (NO)
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? (YES) NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES (NO)
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
  NOTE: Form 3454 was submitted for all investigators certifying that no investigator had anything to disclose, therefore Form 3455 was not submitted.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES (NO)
  NOTE: No CMC Section

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? (YES) NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
  Yes

- List referenced IND numbers: IND 37,522

- End-of-Phase 2 Meeting(s)? Date(s) _____ (NO)
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? **Pre-sNDA meeting** Date(s) June 24, 2002 NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES (NO)

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES (NO)

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES (NO)

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  (N/A) YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  (N/A) YES NO

- Has DOTCDP been notified of the OTC switch application? (N/A) YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  (N/A) YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES (NO)

If no, did applicant submit a complete environmental assessment? YES (NO)
If EA submitted, consulted to Nancy Sager (HFD-357)? YES (NO)

- Establishment Evaluation Request (EER) submitted to DMPQ? YES (NO)

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES (NO)

NOTE: No chemistry section

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 12, 2004

BACKGROUND: Monistat 1 Combination Pack was approved June 29, 2001. Non-prefilled and pre-filled applicator versions of this product were approved at a later date (S-004 & S-005) respectively. The product was approved with directions for use to insert the drug product "at bedtime". This supplement was submitted to remove that "at bedtime" and allow for product use day or night.

ATTENDEES: Charley Ganley, Curtis Rosebraugh, David Hilfiker, Linda Hu, Andrea Leonard Segal, Arlene Solbeck, Helen Cothran, Renata Albrecht, Rigo Roca, Karen Higgins, Shukal Bala, Anne Marie Homonnay Weikel, Ellen Molinaro

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Joette Meyer HFD-590
Secondary Medical:	Linda Hu HFD-560
Statistical:	Karen Higgins HFD-590
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	Kalamati Suvarna HFD-590
DSI:	
Interdisciplinary Scientist (Reviewer):	Arlene Solbeck HFD-560
Regulatory Project Management:	Leah Cutter HFD-560 & Anne Marie Weikel HFD-590

Other Consults:

Per reviewers, are all parts in English or English translation? (YES) NO
If no, explain:

CLINICAL FILE __X__ REFUSE TO FILE _____

- Clinical site inspection needed: YES (NO)
- Advisory Committee Meeting needed? YES, date if known _____ (NO)
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? (N/A) YES NO

CLINICAL MICROBIOLOGY	NA _____	FILE __X__	REFUSE TO FILE _____
STATISTICS		FILE __X__	REFUSE TO FILE _____
BIOPHARMACEUTICS	NA __X__	FILE _____	REFUSE TO FILE _____
• Biopharm. inspection needed:			YES NO
PHARMACOLOGY	NA __X__	FILE _____	REFUSE TO FILE _____
• GLP inspection needed:			YES NO
CHEMISTRY	NA __X__	FILE _____	REFUSE TO FILE _____
• Establishment(s) ready for inspection?			YES NO
• Microbiology			YES NO

ELECTRONIC SUBMISSION:
Any comments: Data on the Phase III study was not submitted electronically

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__X__ Filing issues to be communicated by Day 74. List (optional): Review issues only, additional information requested

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-560

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/s/

Leah Cutter
1/20/04 11:37:36 AM
CSO

MEMORANDUM OF TELECON

DATE: January 12, 2004

BETWEEN:

Name: Terry Glass, Esq.
Director, Regulatory Affairs

Representing: Personal Products Company (PPC)

AND

Name: Leah Cutter, Ph.D., Regulatory Project Manager
Division of Over-the-Counter Drug Products, HFD-560

APPLICATION: NDA 21-308 S-009

DRUG: Monistat 1 Combination Pack (miconazole nitrate 1200 mg vaginal insert and 2 % cream)

SUBJECT: Relay of information requests from filing meeting

The call was initiated by Leah Cutter following the Agency's internal filing meeting. The purpose of the call was to convey the potential review issues to PPC and to request additional information related to these issues.

In the filing review, the following potential review issues were identified:

1. The data for the clinical study was not submitted electronically.

2. The labeling for the product pouch was not submitted.

These comments were provided to give PPC preliminary notice of potential review issues. The filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during the review. Issues may be added, deleted, expanded upon, or modified as the application is reviewed.

PPC was requested to provide the following information:

1. The data for the clinical study in SAS transport file format.

2. The product pouch labeling in .pdf format.

3. Approved product labeling in Word format indicating the proposed changes with strikeout (deletion) and underline (addition).

Summary:
PPC agreed to submit the requested information to the NDA.

Minutes Preparer:

{See appended electronic signature page}

Leah Cutter, Ph.D.
Regulatory Project Manager
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

Leah Cutter
1/28/04 03:57:20 PM
CSO

MEMORANDUM OF TELECON

DATE: August 3, 2004
August 11, 2004

BETWEEN:

Name: Terry Glass, Esq.
Director, Regulatory Affairs

Kathy Davino
Associate Director, Regulatory Affairs

Representing: Personal Products Company (PPC)

AND

Name: Leah Cutter, Ph.D., Regulatory Project Manager
Division of Over-the-Counter Drug Products, HFD-560

APPLICATION: NDA 21-308 S-009

DRUG: Monistat 1 Combination Pack (miconazole nitrate 1200 mg vaginal insert and 2 % cream)

SUBJECT: Request for additional data

The call was initiated by Leah Cutter. The purpose of the call was to convey a request for additional information from the FDA's clinical reviewer to PPC.

During the call, PPC was requested to provide tables of adverse events for patients grouped by age (< 65 years of age and >= 65 years of age) and race (i.e. Caucasian, Black, and Hispanic). It was requested that the tables be formatted like Table 20 in the study report for study CA-P-2343-2 and be sent in electronic format (i.e. pdf files).

Summary and Action Items:
PPC agreed to submit the information as requested above.

Minutes Preparer:

{See appended electronic signature page}

Leah Cutter, Ph.D.
Regulatory Project Manager
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Leah Cutter
8/19/04 08:49:23 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-308/S-009

CORRESPONDENCE

NDA NO. 21-308 REF NO. 004
NDA SUPPL FOR SE8

Personal Products
COMPANY

DIVISION OF McNEIL-PPC, INC.
199 Grandview Road
Skillman, New Jersey 08558

RECEIVED
DEC 0 3 2003
MEGA/CDER

December 2, 2003

Charles Ganley, M.D., Director
Division of Over the Counter Drug Products (HFD-560)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: Prior Approval Supplement
NDA 21-308
MONISTAT® 1 Combination Pack (miconazole nitrate vaginal insert 1200mg and miconazole nitrate cream 2%)

Dear Dr. Ganley:

Reference is made to our New Drug Application, NDA 21-308 for MONISTAT® 1 Combination Pack (miconazole nitrate vaginal insert 1200 mg and miconazole nitrate cream 2%). In accordance with 21 CFR§314.70, Personal Products Company (PPC) is submitting a Prior Approval Supplement. Reference is also made to IND 37,522 Amendment Serial Number 084, filed November 19, 2002, which included Protocol # CA-P-2343, "A Multi-centered, Randomized, Parallel-group, Investigator-blinded Study to Compare the Safety and Efficacy of MONISTAT® 1 Combination Pack in Bedtime versus Daytime Administration." The objective of this study was to change the labeled directions for MONISTAT® 1 Combination Pack.

The results of this study are being submitted for approval to change the label instructions to allow for daytime administration of the drug product in addition to the current bedtime administration. The instructions are being changed by removing the words "at bedtime" (regarding vaginal insertion) in the current labeling for both the non-prefilled MONISTAT® 1 Combination Pack (NDA 21-308 Original Submission) and the prefilled applicator MONISTAT® 1 Combination Pack (S-004/S-005) versions of this product. Draft labeling of the carton and insert for both product versions is included in this submission.

ORIGINAL

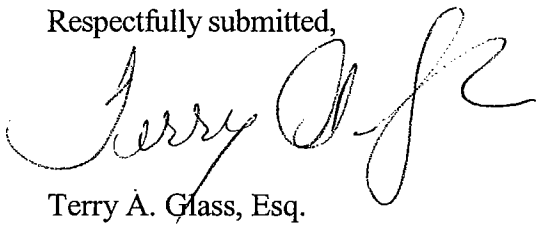
Additionally, the required user fee of $ 286,750.00 was sent under separate cover to the FDA, Philadelphia, PA address on November 11, 2003 (User Fee ID# 4646).

Please refer to the Overall Reviewer's Guide located in the first volume (Vol. 1.1) of this supplement for information regarding the organization of this submission. Item 12 of this supplement is provided in electronic format only. We have also included the clinical/statistical sections of the supplement and the draft labeling on a CD ROM for your convenience.

The material and data herein are considered confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 3310.

Should you have comments or questions regarding this submission, please contact me directly at 908-904-3762.

Respectfully submitted,



Terry A. Glass, Esq.
Director, Regulatory Affairs
Personal Products Company

cc: Leah Cutter, Project Manager (DOTCDP, HFD-560)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Personal Products Company	December 2, 2003
TELEPHONE NO. *(Include Area Code)* (908) 904-3762	FACSIMILE (FAX) Number *(Include Area Code)* (908) 904-3748
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 199 Grandview Road, Room SF101 Skillman, New Jersey 08558	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*
21-308

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
miconazole nitrate, USP	MONISTAT® 1 Combination Pack

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
1-[2,4-dichloro-β(dichlorobenzyloxy) phenethyl] imidazole	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
vaginal insert & cream	1200mg insert & 2% cream	intravaginal and external

(PROPOSED) INDICATION(S) FOR USE:
Treatment of vulvovaginal candidiasis and relief of external vulvar irritation

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (NDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☒ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION
Removal of bedtime use instructions from labeling, product can be used day or night.

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC ☐

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

ORIGINAL

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 37,522 Miconazole Nitrate Suppositories

RECEIVED
DEC 03 2003
MEGA/CDER

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Terry A. Glass	Terry A. Glass, Esq. Director, Regulatory Affairs	12/2/2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
199 Grandview Road, Room SF101 Skillman, New Jersey 08558	(908) 904-3762

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/03)

Prior Approval Supplement
NDA 21-308
MONISTAT® 1 Combination Pack
OVERALL REVIEWERS GUIDE

Archival Copy
The archival copy (blue) of this application consists of consecutively numbered volumes distributed as follows:

Item		NDA Volume(s)
1	Index	1.1
2	Application Summary	1.1
4c	Draft Labeling	1.1
8/10	Clinical Data/Statistical Data	1.2
11	Data Listings	1.3, 1.4, 1.5
12	Case Report Forms	Provided Electronically (no hard copy provided)

Review Copy
The review copy of this application contains each technical section separately bound in the appropriate FDA binders as follows:

Review Discipline	Contains NDA Items	NDA Volume(s)
Clinical	1, 2, 4c	1.1
	8/10	1.2
	11	1.3, 1.4, 1.5
	12	Electronic
Statistics	1, 2, 4c	1.1
	8/10	1.2

Desk Copies
12 Desk Copies of Items 1, 2, 4c (contained in volume 1.1) and 4 Desk Copies of Item 11 (contained in volumes 1.3, 1.4, 1.5)

Items 12: In electronic format only - 3 desk copies, one archive copy, and one copy to electronic document room.

Prior Approval Supplement
NDA 21-308
MONISTAT® 1 Combination Pack
OVERALL REVIEWERS GUIDE

Indexing

The index for the entire submission is titled Table of Contents and is provided as Item 1 and included in Volume 1.1 of this submission. The Review Copy is provided Volume 1.1 as a separate volume.

Each individual item of this submission has its own detailed Table of Contents. The appropriate individual Table of Contents is provided behind the first tab in each volume of each item. For example, Item 11: Table of Contents is located behind the first tab of Vol 1. (pp. 11-000001 – 11-000002) and again behind the first tab of Vol. 1.3 (exact duplicate of pp. 11-000001 – 11-000002).

Page Numbering System

Each NDA page number consists of 2 parts, as follows:

11	000001
The first two digits represent the item number.	The last six digits represent the Page Number within the given item.

The pages within each item are numbered consecutively beginning with number 000001. The page numbers appear in the lower right hand corner of each page in this submission.

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MONISTAT® 1 Combination Pack
ITEM 1: TABLE OF CONTENTS

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Item	Description	Volume	Page
12	**CASE REPORT FORMS FOR PATIENTS THAT DISCONTINUED AS A RESULT OF ADVERSE EXPERIENCES Table of Contents**		

This section is provided in electronic format only.

Protocol Number: CA-P-2343-P

"A Multi-centered, Randomized, Parallel-group, Investigator-blinded Study to Compare the Safety and Efficacy of MONISTAT® 1 Combination Pack in Bedtime versus Daytime Administration"

Study Site	Subject Number	Treatment
1154-1/ [redacted]	66608	Daytime Treatment
1183-1/ [redacted]	60508	Nighttime Treatment
1186-1/ [redacted]	54206	Daytime Treatment
1201-1/ [redacted]	64706	Nighttime Treatment
1232-1/ [redacted]	58306	Nighttime Treatment
1232-1/ [redacted]	75107	Nighttime Treatment
1277-1/ [redacted]	59506	Nighttime Treatment
1301-1/ [redacted]	57507	Daytime Treatment
1320-1/ [redacted]	57706	Daytime Treatment
1331-1/ [redacted]	56207	Nighttime Treatment

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ON ORIGINAL

Prior Approval Supplement
NDA 21-308
MONISTAT® 1 Combination Pack
ITEM 4c: Labeling

Personal Products Company (PPC) has included herein the draft labeling for this submission. Please find enclosed the proposed product cartons and package inserts for both MONISTAT® 1 Combination Pack and MONISTAT® 1 Combination Pack with Prefilled Applicator. The carton and package insert for MONISTAT® 1 Combination Pack with Prefilled Applicator is based on the expected approval of the labeling currently under review in NDA 21-308/S-008, in addition to the proposed changes in this supplement. The product pouch and 9 gram tube of external cream remain unchanged by this supplement, and therefore, have not been included.

The changes are follows:

Product Cartons: Updated Front Panel Graphics

Drug Fact Boxes: Changed Third Bullet in "Directions" from "**vaginal insert:** with the applicator place the vaginal insert into the vagina at bedtime. Throw applicator away after use." to "**vaginal insert:** with the applicator place the vaginal insert into the vagina. Throw applicator away after use."

On the print out of the non-prefilled applicator product carton some of the section headings contain incorrect spacing. This spacing issue is due to the printer used for the hard copies and will not be present on the final labeling.

Package Inserts:

- On back panel, first column, first bullet changed "Use the Applicator containing the OVULE™ Insert at bedtime, even during your menstrual period." to "Use the Applicator containing the OVULE™ Insert, even during your menstrual period."
- In the Instructions for Use section removed "Begin treatment before going to bed:"
- Added product use instructions for women who choose to stand during product insertion, "Gently insert the applicator into the vagina as far as it will go comfortably. This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture."
- Removed last instruction "Lie down as soon as possible after inserting the OVULE™ Insert. This will reduce leakage."
- In the Direction for using the External Vulvar Cream changed instruction 5 from, "Repeat steps 2 – 4 each morning and at bedtime for up to 7 days, as needed." to "Repeat steps 2 – 4, up to two times daily, as needed."

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-308/S-009

Personal Products Company
Attention: Terry Glass, Esq.
Director, Regulatory Affairs
199 Grandview Road, Room SF101
Skillman, NJ 08558

Dear Ms. Glass:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Monistat 1 Combination Pack (miconazole nitrate 1200 mg vaginal insert and 2 % cream)

NDA Number: 21-308

Supplement number: 009

Date of supplement: December 2, 2003

Date of receipt: December 3, 2003

This supplemental application proposes to change the labeling instructions to allow for daytime administration of the drug product in addition to the current bedtime administration.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 1, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be October 3, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric populations unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room HFD-560
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room HFD-560
9201 Corporate Blvd
Rockville, Maryland 20850-3202

If you have any question, call Leah Cutter, Ph.D., Regulatory Project Manager, at (301) 827-2248.

Sincerely,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Hilfiker
12/15/03 03:53:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-308/S-009

DISCIPLINE REVIEW LETTER

Personal Products Company
Attention: Terry Glass, Esq.
Director, Regulatory Affairs
199 Grandview Road, Room SF101
Skillman, NJ 08558

Dear Ms. Glass:

Please refer to your December 2, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monistat 1 Combination Pack (miconazole nitrate 1200 mg vaginal insert and 2 % cream).

Our review of the Labeling section of your submission is complete, and we have identified the following deficiencies:

A. Carton and Drug Facts:

1. Non-prefilled SKU: Bold the word "printed" in the first bulleted statement in ***Other information*** to be consistent with the carton labeling.

2. Non-prefilled SKU:
   - Remove the extra space between the "F" and "a" in "*Drug Facts*".
   - Remove the extra space between "*Drug Facts*" and "(continued)".
   - Left justify "***Directions***".
   - Remove the extra space between "Other" and "information" in "***Other information***".
   - Remove the extra space between the "I" and "nactive" in "***Inactive ingredients***" and between both words of the subheading.
   - Remove the extra spaces between the "Q" and "uestions?" in "***Questions***"
   - Delete the space between the third and fourth bulleted statements under "**Ask a doctor before use if you have**".

3. Both SKUs: Realign the "e" in "***Purpose***" with the last "l" in "Vaginal antifungal".

4. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most

women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

B. Consumer Information Leaflet:

5. Non-prefilled SKU: In the section **How can I get the best results when treating my infection?** the words "at bedtime" were deleted from the first bulleted statement. This is acceptable. However, the statement now reads "Use the Applicator containing the OVULE™ Insert, even during your menstrual period." Since this is not the pre-filled applicator SKU, the statement should read "Use the OVULE™ Insert, even during your menstrual period." Revise this statement.

6. Non-prefilled SKU: Under **What side effects may occur with Monistat ® 1 Combination Pack?**, the first sentence reads "A mild increase in vaginal burning, itching, or irritation may occur when the Applicator containing the OVULE™ Insert is inserted." Since this in not the prefilled applicator, the statement should read "A mild increase in vaginal burning, itching, or irritation may occur when the OVULE™ Insert in inserted."

7. Both SKUs:
   - For the prefilled SKU: Under **Directions for using the Applicator containing the Ovule™ Insert**, the second and third sentences of direction #3 were revised to read "This can be done while standing with your feet spread a few inches apart and your knees bent. Or, you can lie on your back with your knees bent. As shown in the picture." This is acceptable, except we would recommend "As shown in the picture" to be part of the sentence "or, you can lie on your back with your knees bent."
   - For the non-prefilled SKU: Revise the same direction. It is direction #5.

8. Non-prefilled SKU: Under ***Other information***, revise the Tamper-Evident Unit statement to be consistent with the carton and Drug Facts labeling (e.g. "**TAMPER-EVIDENT UNIT – do not use if printed sealed pouch or sealed vaginal insert blister is torn, open or incompletely sealed**").

9. Both SKUs: Add the following "expectation of benefit for 1-day products" under ***Other information*** to read as follows: "[bullet] this is a 1-dose treatment. Most women do not get complete relief of their symptoms in just 1 day. Most women get some improvement in 1 day and complete relief by 7 days."

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Leah Cutter, Ph.D., Regulatory Project Manager, at 301-827-2248.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Curtis Rosebraugh
8/3/04 02:53:18 PM