

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-670 / S-014

Name: Monistat[®] 3 Combination Pack

Sponsor: Personal Products Company

Approval Date: March 16, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

APPROVAL LETTER



NDA 20-670/S-014

Personal Products Company
Attention: Renee L. Alliegro
Manager, Regulatory Affairs
199 Grandview Road
Skillman, NJ 08558-9418

Dear Ms Alliegro:

Please refer to your supplemental new drug application dated November 16, 2006, received November 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Monistat 3-Combination Pack (200 mg, miconazole nitrate vaginal suppositories and 2% miconazole nitrate cream).

We acknowledge receipt of your submissions dated November 8, and November 16, 2006, and March 16, 2007.

This supplemental new drug application provides for an alternate preparation of the vaginal suppository as a gelatin-encapsulated vaginal suppository, and associated labeling changes.

We have completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical to, and include the revisions indicated, to the enclosed labeling (carton and Drug Facts labeling and Consumer Information Leaflet submitted March 16, 2007) and must be in the "Drug Facts" format (21 CFR 201.66) where applicable. These revisions are terms of the approval of this application. Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL 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 but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement "NDA 20-670/S-014."** Approval of this submission by FDA is not required before the labeling is used.

We remind you to remove the flag "New!" 6 months after introduction into the marketplace.

NDA 20-670/S-014

Page 2

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 Mary Lewis, Regulatory Project Manager, at (301) 796-0941.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, MD
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Joel Schiffenbauer
3/16/2007 03:03:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

LABELING



Miconazole Nitrate (200 mg) Gelatin-
Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

The secondary packaging process is that the sealed foil pouches, disposable applicators, one 9g tube of Miconazole Nitrate Cream (2% w/w), and consumer information leaflet will be placed into a folding carton, which will be glue-sealed on the end flaps.

4.7 Drug Product Labeling

Labeling for the proposed product, Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository, will be in accordance with regulations governing drug product labeling, and as such, the Drug Facts portion of the folding carton will remain mostly unchanged from the currently approved MONISTAT[®] 3 Vaginal Suppository, as per NDA 20-670. The product name of "MONISTAT[®] 3 Combination Pack" will remain unchanged, although the new product is an additional packaging configuration to the currently approved and marketed MONISTAT[®] 3 unencapsulated vaginal suppositories. In alignment with the dosage form descriptor for MONISTAT[®] 1 Combination Pack, PPC proposes to refer to the new product dosage form as an "OVULE[®] Insert".

The following is the text proposed for the new product carton.

Principal Display Panel

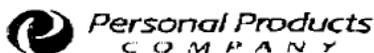
MONISTAT[®] 3 Combination Pack
Miconazole Nitrate Vaginal Inserts (200 mg) and Miconazole Nitrate Cream (2%)
(inside blue banner at top of PDP)

VAGINAL ANTIFUNGAL
CURES MOST VAGINAL YEAST INFECTIONS
AND RELIEVES ASSOCIATED EXTERNAL ITCHING AND IRRITATION
(center of PDP, white background)

3 OVULE[®] Inserts With 3 Applicators plus External Cream *(center, bottom box)*

Net Wt. = 3 Ovule[®] Inserts + 0.32 oz. (9 g) tube *(bottom right corner)*

[Image of Ortho symbol] *(bottom left corner)*



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

Drug Facts Box

MONISTAT® 3
COMBINATION PACK
Miconazole Nitrate Vaginal Insert (200 mg) and Miconazole Nitrate Cream (2%)
Vaginal Antifungal

Drug Facts

Active ingredients

Purpose

Miconazole nitrate 200 mg (in each 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 and 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 discharge

If pregnant or breastfeeding, 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.



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

Drug Facts Box (continued)

Directions

- before using this product read the enclosed consumer information leaflet for complete directions and information *delete BB 3/15/07*
- adults and children 12 years of age and over:
 - vaginal insert:** with a disposable applicator place the ~~(b)(4)~~ 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

at bedtime

Other Information

- do not use if printed sealed pouch containing vaginal insert *add "s" are BB 3/15/07* 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)

Inactive ingredients

- vaginal insert: gelatin, glycerin, titanium dioxide, hydrogenated vegetable oil base *BB 3/15/07*
- 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

5th Panel

New! (in flag, top left corner)
Combination Pack 3 Day Treatment ~~(b)(4)~~ *moved to the center larger type size*

~~(b)(4)~~ *delete*
~~(b)(4)~~ (center or left placement on panel) *BB 3/15/07*

3 Ovule® Inserts with 3 Applicators to Treat
Plus External Cream for Itch Relief (on right side of panel)

[Image of 3 ovules, 3 applicators, and tube of external cream] (on right side of panel)

See attachment for 5th panel delete

Bottom Flap:

TAMPER-EVIDENT UNIT DO NOT USE IF PRINTED SEALED POUCHES ARE TORN, OPEN, OR INCOMPLETELY SEALED

Bolded BB 3/15/07



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

Consumer Information Leaflet

MONISTAT[®] 3 COMBINATION PACK

Miconazole Nitrate Vaginal Insert (200 mg) and Miconazole Nitrate Vaginal Cream (2%)

VAGINAL ANTIFUNGAL

Cures Most Vaginal Yeast Infections and Relieves Associated External Itching and Irritation

Why should I use MONISTAT[®] 3 Combination Pack?

MONISTAT[®] 3 Combination Pack contains 3 OVULE[®] Inserts that cure 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[®] 3 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[®] 3 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).

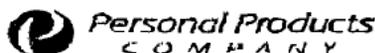
How can I tell if I have a vaginal yeast infection?

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.

3/15/07



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
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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[®] 3 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



Miconazole Nitrate (200 mg) Gelatin-
Encapsulated Vaginal Suppository
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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® 3 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® 3 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® 3 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® 3 Combination Pack.
- Condoms and diaphragms may be damaged by this product and fail to prevent pregnancy or sexually transmitted diseases (STDs).

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

- Use 1 OVULE® Insert at bedtime, even during your menstrual period for 3 nights in a row.
- 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® 3 Combination Pack.
- Do not have vaginal intercourse while using MONISTAT® 3 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® 3 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.



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

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

- *If you do not get complete relief ask a doctor before using another product*

How Should I Use MONISTAT[®] 3 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 ³ Applicator[®] and 3 OVULE[®] Inserts:

Begin treatment before going to bed:

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

2. Place the OVULE[®] Insert firmly into the top (wider end) of the applicator so it will not fall out (see picture).

3. Hold the applicator containing the OVULE[®] Insert by the opposite end from where the OVULE[®] Insert is located.

4. Gently insert the applicator into the vagina as far as it will go comfortably. This can be done while lying on your back with your knees bent (as shown in picture), or while standing with your feet apart and knees bent.

5. 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.

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

7. Lie down as soon as possible after inserting the OVULE[®] Insert. *This will reduce leakage.*

8. Repeat steps 1-7 before bedtime for the next 2 days. You may want to use deodorant-free pads or pantyshields to protect your clothing during the time that you are using MONISTAT[®] 3 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.



Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository
NDA 20-670; Supplemental NDA-014

- 4. Screw the cap back on the tube.
- 5. Repeat steps 2 – 4 each morning and at bedtime for up to 7 days, 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® 3 Combination Pack?

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

Stop using MONISTAT® 3 Combination Pack and consult your doctor if you have abdominal pain, headache, 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® 3 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 **(b) (4)** *pouches are* 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)

Active Ingredients: OVULE® Insert: miconazole nitrate (200mg each OVULE® Insert). External Vulvar Cream: miconazole nitrate 2%

Inactive Ingredients: OVULE® Insert: gelatin, glycerin, titanium dioxide, hydrogenated vegetable oil base. 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
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3/15/07

3/15/07

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1

Rec'd 1/16/07

EXPIRATION DATE

LOT #

VAGINAL ANTIFUNGAL

MONISTAT³
COMBINATION PACK



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

3 OVULE[®] Inserts With
3 Applicators plus External Cream

Net Wt. - 30VULE[®] Inserts +
0.32 oz (9g) tube

VAGINAL ANTIFUNGAL

MONISTAT³
COMBINATION PACK
Miconazole Nitrate Vaginal Inserts (200 mg) and Miconazole Nitrate Cream (2%)

J063216-4816-0

2 If you have any questions or comments, please call 1-877-MONISTAT
(1-877-556-4382) or visit our website at www.monistat.com

VAGINAL ANTIFUNGAL

MONISTAT³
COMBINATION PACK
Miconazole Nitrate Vaginal Inserts (200 mg) and Miconazole Nitrate Cream (2%)

NEW

COMBINATION PACK
3 DAY TREATMENT

3 Day OVULE[®] Insert Treatment

3 OVULE[®] Inserts
With 3 Applicators to Treat
Plus External Cream for Itch Relief!

MONISTAT³
COMBINATION PACK

Miconazole Nitrate Vaginal Inserts (200 mg) and Miconazole Nitrate Cream (2%)

VAGINAL ANTIFUNGAL

OPEN HERE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

DIVISION DIRECTOR'S MEMO



CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
301.796.2280

MEMORANDUM

Date: March 16, 2007

From: Joel Schiffenbauer, M.D.
Deputy Director, DNCE

Subject: NDA 20-670/S-014
Monistat 3

Sponsor: Personal Products Company

The Prior Approval Supplement requests approval for an alternate preparation of the vaginal suppository, namely as a gelatin-encapsulated suppository, that will be included in the Monistat 3 Combination Pack. In this chemistry supplement, the applicant proposes to coat the Monistat 3 vaginal suppository with gelatin. The proposed product is composed of two parts: the wax suppository mass and the gelatin shell. The amount of active ingredient, Miconazole Nitrate, USP, will not be altered and the excipients for the wax suppository portion of the proposed product will remain unchanged from the approved, non-encapsulated suppository. The material for use in manufacturing the gelatin shell is the same as that used to manufacture the approved Monistat 1. Historically, the Monistat 1 product utilizes the same gelatin coating, and clinical studies at the time of approval showed that that product is effective with a gelatin coating.

To support the change the applicant submitted chemistry studies including disintegration and dissolution testing and new labeling. The reader is referred to the chemistry review for details. Of note, the chemistry group met with the applicant in December 2005 and agreed with the in vitro approach taken by the applicant (see meeting minutes in DFS, signed 12/20/2005 by Dr. Patel).

According to the chemistry review, the changes are acceptable from a chemistry perspective. Both products dissolve about (b) (4) over 24 hours at 37 degrees centigrade.

However, in this submission there was no new clinical data submitted by the sponsor to support the efficacy of the new change, and the question was raised as to whether clinical data would be needed to support the present change. On March 14, 2007 a discussion between members of DNCE and Special Pathogens group (including Steven Gitterman and Renata Albrecht and others) ensued. It was commented that the usual standard is for clinical trials to be performed, that these studies serve as “bioequivalence” studies for topical vaginal products, and that the Agency recommends clinical studies in circumstances where there are product changes. However, several arguments were made as to why additional clinical studies were not needed for this product change (and these comments reflect the opinion of most of the participants at the meeting):

1. The change is from a non-gelatin encapsulated suppository to a gelatin encapsulated suppository. The actual formulation of the active ingredient is not altered in this situation; the percentage and composition of the active component of the product is unchanged.
2. The disintegration of the encapsulated suppository is acceptable to the chemists and is comparable to the disintegration of the non-encapsulated suppository that was originally approved and the tests were conducted under the same conditions.
3. The dissolution profile of the non-encapsulated and the encapsulated suppositories is similar, if not identical at (b) (4) .

Based on the above assertions it was concluded that it would not be expected that the 2 suppositories would behave differently in terms of efficacy.

Dena Hixon in the Office of Generic Drugs commented in a subsequent e-mail communication that the standard for a generic approval would be to require a clinical study because of concerns that there is no in vitro/ in vivo correlate, and it is not known how the new product will behave in the vaginal environment (some participants at the 3/14/07 meeting also agreed that this was a concern). However, she wrote that she also spoke with Dale Conner the Director of Division of Bioequivalence, who commented that the Agency sometimes does accept a dissolution approach to encapsulating an approved oral product.

Based on the above discussions and arguments and on the previous agreements reached between the chemistry group and the company in 2005, and after discussion with Dr. Leonard-Segal, it was decided to approve the requested change

to this product. Going forward, further discussions are needed to consider the approach taken for this specific change as described in this supplement, and whether the Agency will continue to follow the same path or require clinical studies for future product changes, will need to be addressed, possibly on a case by case basis. It is my recommendation that the approach taken by OGD, to ask for clinical studies, be the generally accepted approach.

There are additional labeling changes that are pending at the time of this writing, that need to be resolved (see labeling review). If these can be resolved I recommend approval.

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this page is the manifestation of the electronic signature.**

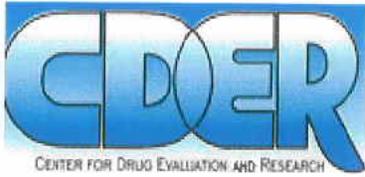
/s/

Joel Schiffenbauer
3/16/2007 12:46:10 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

LABELING REVIEWS



ONP Drug Labeling Review

Office of Nonprescription Products

Center for Drug Evaluation and Research • Food and Drug Administration

NDA#: 20-670/S-014

Submission Date: November 16, 2006

Type of Submission: Prior Approval Supplement-Chemistry, Manufacturing and Controls

Sponsor: Personal Products Company (PPC), Division of McNeil-PPC, Inc.

Drug Product: Monistat® 3 (miconazole nitrate) Combination Pack

Active Ingredient:

- Miconazole nitrate 200 mg (in each OVULE® Insert)
- Miconazole nitrate 2% (external cream)

Indications:

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

Stock Keeping Units: one (1); 3 disposable applicators and 3 Ovule® Inserts plus one 9 gram tube external vulvar cream

Review Date: March 2, 2007

Reviewer: Arlene Solbeck
Division of Nonprescription Regulation Development

Project Manager: Mary Lewis
Division of Nonprescription Clinical Evaluation

Background

NDA 20-670, Monistat® 3 Combination Pack, was approved as an over-the-counter (OTC) vaginal drug product by FDA on April 16, 1996. It is a three-day treatment consisting of one miconazole nitrate suppository per night for three consecutive nights

(200 mg in each suppository) along with miconazole nitrate external vulvar cream (2%) as needed. The last annual report submitted to FDA (May 1, 2006) contained labeling for a disposable applicator SKU and a reusable applicator SKU. The sponsor is requesting, by submitting this current chemistry supplement (S-014), to market an alternate preparation of the miconazole nitrate vaginal suppository which is a gelatin-encapsulated vaginal suppository (which the sponsor is calling an OVULE® Insert) that will be made available as an alternative option to consumers in addition to the existing approved Monistat® 3 Combination Pack. The sponsor is currently marketing a soft gel vaginal insert (which they also call an OVULE® Insert) as Monistat® 1 Combination Pack under NDA 21-308 and is a single application, miconazole nitrate (1200mg) soft gel vaginal insert with 2% miconazole nitrate cream for external use as needed. The 1200 mg Monistat Ovule® Insert was approved for OTC use on June 29, 2001. On October 1, 2004, FDA approved the 1200 mg Ovule® Insert for daytime administration in addition to the current bedtime administration. It is our understanding that the 200 mg Ovule® Insert proposed by the sponsor in this submission is not intended for day time administration.

The sponsor sent the following labeling for review:

- Carton (PDP, Drug Facts, Fifth Panel)
- Consumer Information Leaflet
- Foil Pouch

Reviewer's Comments

PPC states in the submission that the labeling for the proposed product, Miconazole Nitrate (200 mg) Gelatin-Encapsulated Vaginal Suppository, will remain mostly unchanged from the currently approved MONISTAT® 3 Vaginal Suppository, as per NDA 20-670. The product name of MONISTAT® 3 Combination Pack will remain unchanged, although the new product is an additional packaging configuration to the currently approved and marketed MONISTAT® 3 unencapsulated vaginal suppositories. PPC also states that in accordance with the dosage form descriptor for MONISTAT® 1 Combination Pack, they propose to refer to the new product form as an "OVULE® Insert." FDA notes that the carton labeling (Drug Facts) and the Consumer Information Leaflet sent by the sponsor electronically are blurry and the text is not uniform. The sponsor stated that it happens when documents are scanned into/manipulated in Adobe and they don't expect to see this in the final printed labeling.

I. Carton and Drug Facts Labeling

A. Principal Display Panel (PDP)

- The PDP is acceptable. PPC refers to the dosage form on the PDP as "3 Ovule® Inserts" which is acceptable. PPC identifies the OVULE® Inserts as containing 200 mg miconazole nitrate, so there shouldn't be any confusion with the MONISTAT® 1 OVULE® Inserts.

B. Drug Facts

1. Under **Active ingredients**, "Miconazole nitrate 200 mg (in each vaginal insert)" replaces "Miconazole nitrate (200 mg in each suppository)". This is acceptable. Vaginal insert is also used in the statement on identity on the PDP. It is also used in the Monistat® 1 carton labeling.
2. Under **When using this product**, the sponsor added a fourth bulleted statement in accordance with a letter to the sponsor dated 12/12/06 from FDA which provides for a class labeling change. The bullet reads "if you do not get complete relief ask a doctor before using another product". This is acceptable.
3. Under **Directions**, remove the period from the first bulleted statement.
4. Under **Directions**, "Vaginal Insert" replaces "Suppositories" in the first sub-bullet under the second bulleted statement. The sponsor should revise "Vaginal Insert" in the first sub-bullet to read "vaginal insert" as well as revise "External Cream" in the second sub-bullet to read "external cream". In the first sub-bullet, "applicator" replaces "disposable applicator". This is acceptable.
5. Under **Directions**, in the first sub-bullet under the second bulleted statement, revise "with a disposable applicator place the insert into the vagina." to read "with a disposable applicator place the insert into the vagina at bedtime." to be consistent with prior approved labeling.
6. Under **Other information**, the Tamper-Evident Statement for the vaginal insert (first bulleted statement) was revised to read "do not use if printed sealed pouch containing vaginal insert is torn, open, or incompletely sealed". This is acceptable with two exceptions:
 - a. bold the word "printed".
 - b. revise the phrase "if printed sealed pouch containing vaginal insert is" to "if printed sealed pouches containing vaginal inserts are" to be consistent with the Tamper-Evident Warning on the carton bottom.
7. Under **Inactive ingredients**, the inactive ingredients for the vaginal insert should be in alphabetical order (e.g., move hydrogenated vegetable oil).

C. Fifth Panel

1. The flag containing the word New! should be removed after 6 months of marketing.
2. The phrase '(b) (4)' is promotional and should be deleted.
3. Under '(b) (4)', remove the words '(b) (4)' '(b) (4)'. Effectiveness claims other than "Cures Most Vaginal Yeast Infections"

have not been allowed in the past for any of the other OTC vaginal antifungal drug products.

D. Bottom Flap

- The bottom flap of the carton contains the Tamper-Evident Statement which, for this product, reads "TAMPER-EVIDENT UNIT DO NOT USE IF PRINTED SEALED POUCHES ARE TORN, OPEN, OR INCOMPLETELY SEALED". This is acceptable with one exception: bold the word "PRINTED".

II. Consumer Information Leaflet

PPC stated in their submission that the Consumer Information Leaflet (CIL) was revised to reflect the new form and shape of the proposed product (ovule).

1. PPC revised the statement of identity on the Consumer Information Leaflet by replacing the word "Suppository" with "Vaginal Insert". This is acceptable.
2. Under "Why should I use MONISTAT® 3 Combination Pack?", the phrase that begins "MONISTAT® 3 Combination Pack contains 3 suppositories" was revised to read "MONISTAT® 3 Combination Pack contains 3 OVULE® Inserts". This is acceptable.
3. Under "Why should I use MONISTAT® 3 Combination Pack?", underline the word "first" in the second bolded statement which reads: "*See your doctor or health professional first to find out the cause of your symptoms.*" This is consistent with prior approved labeling.
4. Under "Can I use other vaginal products with MONISTAT® 3 Combination Pack?", the word "suppository" in the first bulleted statement was changed to "OVULE® Insert". This is acceptable.
5. Under "How can I get the best results when treating my infection?", the words "vaginal suppository" in the first bulleted statement were changed to "OVULE® Insert". This is acceptable.
6. Under "What warnings should I know about when using MONISTAT® 3 Combination Pack", under "When using this product", add a fourth bulleted statement to read: "if you do not get complete relief ask a doctor before using another product", to be consistent with Drug Facts.
7. Under "How Should I Use Monistat® 3 Combination Pack?", the following changes were made:
 - a. The subheading "Directions for using the 3 Vaginal Suppositories" was revised to "Directions for using the Applicator and 3 OVULE® Inserts".

- This is acceptable with one exception: change the word "Applicator" to "Applicators".
- b. Direction #1 was revised to read "Open pouch and remove contents (see picture). KEEP CONTENTS DRY BEFORE USE. OPEN POUCH JUST BEFORE USE." in accordance with the change from suppository to OVULE® Insert. This is acceptable.
 - c. In direction #2 the words "OVULE® Insert" replace "suppository". This is acceptable.
 - d. In direction #3, the words "OVULE® Insert" replace "suppository" in two places. This is acceptable.
 - e. In direction #5, the words "OVULE® Insert" replace suppository. This is acceptable.
 - f. In direction #6, the direction for reusable applicators was deleted. This is acceptable since this product uses disposable applicators.
 - g. In direction #7 the words "OVULE® Insert" replace "suppository". This is acceptable. Add the sentence "This will reduce leakage." after the first sentence in direction #7 which reads "Lie down as soon as possible after inserting the OVULE® Insert." This is consistent with prior labeling for products applied at bedtime.
 - h. In direction #8, the words "OVULE® Insert" replace "suppository". This is acceptable.
8. Under "What side effects may occur with MONISTAT® 3 Combination Pack?", the words "OVULE® Insert" replace "suppository". This is acceptable.
 9. Under "Other Information:"
 - a. The Tamper-Evident Statement was revised to read "TAMPER-EVIDENT UNIT - do not use if printed sealed pouch is torn, open or incompletely sealed. This is acceptable with one exception: change the words "pouch is" to "pouches are" (plural) to be consistent with carton labeling
 - b. Add the embossed design symbol to the second bulleted statement.
 10. Under "Active Ingredients" and "Inactive Ingredients", the words "OVULE® Insert" replace "suppository". This is acceptable.
 11. List the inactive ingredients in alphabetical order (e.g., relocate hydrogenated vegetable oil).

III. OVULE® Insert Pouch

No changes needed. The OVULE® Insert pouch labeling is acceptable.

Reviewer's Recommendations

The following comments can be conveyed to the sponsor:

I. Carton and Drug Facts Labeling

A. Principal Display Panel (PDP)

- The PDP is acceptable.

B. Drug Facts

1. Under *Directions*, remove the period from the first bulleted statement.
2. Under *Directions*, under the second bulleted statement, under the first sub-bullet, revise "**Vaginal Insert:**" to "**vaginal insert:**".
3. Under *Directions*, under the second bulleted statement, under the second sub-bullet, revise "**External Cream:**" to "**external cream:**".
4. Under *Directions*, under the second bulleted statement, under the first sub-bullet, revise "with a disposable applicator place the insert into the vagina." to "with a disposable applicator place the insert into the vagina at bedtime."
5. Under *Other information*, the Tamper-Evident Statement for the vaginal insert (first bulleted statement) was revised to read "do not use if printed sealed pouch containing vaginal insert is torn, open, or incompletely sealed". This is acceptable with two exceptions:
 - a. bold the word "printed" to be consistent with prior approved labeling.
 - b. revise the phrase "if printed sealed pouch containing vaginal insert is" to "if printed sealed pouches containing vaginal inserts are" to be consistent with the Tamper-Evident Warning on the carton bottom.
6. Under *Inactive ingredients*, the inactive ingredients for the vaginal insert should be in alphabetical order (e.g., move hydrogenated vegetable oil).

C. Fifth Panel

7. The flag containing the word New! should be removed after 6 months of marketing.
8. Delete the phrase "(b) (4)", which is promotional.
9. Remove the words "(b) (4)". Effectiveness claims other than "Cures Most Vaginal Yeast Infections" have not been allowed in the past for any of the other OTC vaginal antifungal drug products.

D. Bottom Flap

10. Revise the statement "TAMPER-EVIDENT UNIT DO NOT USE IF PRINTED SEALED POUCHES ARE TORN, OPEN, OR INCOMPLETELY SEALED" by bolding the word "PRINTED" (unless the whole statement is bolded, which is acceptable).

II. Consumer Information Leaflet

11. Under "Why should I use MONISTAT® 3 Combination Pack?", underline the word "first" in the second bolded statement which reads: "*See your doctor or health professional first to find out the cause of your symptoms.*" to be consistent with prior approved labeling.
12. Under "What warnings should I know about when using MONISTAT® 3 Combination Pack", under "When using this product", add a fourth bulleted statement to read: "if you do not get complete relief ask a doctor before using another product", to be consistent with Drug Facts.
13. Under "Directions for using the applicator and 3 OVULE® Inserts", change the word "applicator" to "applicators".
14. Under "Directions for using the applicator and 3 OVULE® Inserts", in direction #7, add the sentence from prior approved labeling which reads: "This will reduce leakage." after the first sentence in direction #7 which reads "Lie down as soon as possible after inserting the OVULE® Insert."
15. Under "Other Information:"
 - a. The Tamper-Evident Statement was revised to read "TAMPER-EVIDENT UNIT - do not use if printed sealed pouch is torn, open or incompletely sealed. This is acceptable with one exception: change the words "pouch is" to "pouches are" to be consistent with carton labeling and Drug Facts.
 - b. Add the embossed design symbol to the second bulleted statement.
16. List the inactive ingredients in alphabetical order (e.g., relocate hydrogenated vegetable oil).

III. OVULE® Insert Pouch

- No changes needed. The OVULE® Insert pouch labeling is acceptable.

Arlene Solbeck, MS
Biologist
Division of Nonprescription
Regulation Development

Helen Cothran, BS
Team Leader
Division of Nonprescription
Regulation Development

Attachments

NDA 20-670/S-014

HFD-590: Weikel/Roca/Meyer/Albrecht/Matecka

ONP: Division File

ONP: Ganley/Segal/Solbeck/Cothran/Hu//Christl/Shay/Lewis/Schiffenbauer

DOCID: 20670s-014.doc

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

/s/

Arlene Solbeck
3/14/2007 04:29:41 PM
INTERDISCIPLINARY

Helen Cothran
3/14/2007 04:40:00 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

CHEMISTRY REVIEWS

Review of Chemistry, Manufacturing, and Controls

Clinical Review Division: Office of Non-Prescription Products

NDA #: 20-670 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 03/15/07

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
N 20670/SCF-014 (PA)	11/16/06	11/17/06	01/04/06

NAME & ADDRESS OF APPLICANT: Personal Products Company (McNeil-PPC, Inc.)
199 Grandview Road
Skillman, NJ 08558

DRUG PRODUCT NAME

Proprietary: Monistat 3 Combination Pack
Nonproprietary/USAN: Miconazole nitrate
Chem.Type/Ther.Class:

Patent Status: NA

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of vaginal yeast infections

DOSAGE FORM: Suppositories (Ovule insert) and Cream

STRENGTHS: Miconazole nitrate, 200mg (suppositories) & 2% (cream)

ROUTE OF ADMINISTRATION: Vaginal

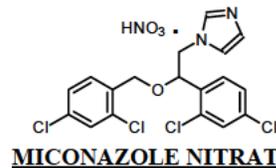
DISPENSED: OTC

PACKAGE SIZES:

SPECIAL PRODUCTS: Yes No (If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Chemical Name: (±)-1-[2,4-Dichloro-β-[2,4-dichloro-benzyl)oxy]phenethyl]imidazole mononitrate
CAS Registry No.: CAS-22832-87-7
Molecular Formula: C₁₈H₁₄Cl₄N₂O • HNO₃
Molecular Weight: 479.14



SUPPORTING DOCUMENTS: Amendments dated 12-DEC-2006 (C) and 08-MAR-2007 (BC)

DMF (b)(4) (as manufactured in (b)(4)), held by (b)(4), Letter of Authorization dated 16-NOV-2006

RELATED DOCUMENTS: NDA 20-968 and NDA 21-308

CONSULTS: NA

REMARKS/COMMENTS:

The Prior Approval Supplement requests approval for an alternate preparation of the vaginal suppository, namely as a gelatin-encapsulated suppository, that will be included in the Monistat 3 Combination Pack. The proposed manufacturing process and equipment are essentially the same as those used to manufacture the other gelatin-encapsulated Monistat 1 (R_x NDA 20-968 and OTC NDA 21-308), although the manufacturing site is different. The proposed product is composed of two parts: the wax suppository mass and the gelatin shell. The amount of active ingredient, Miconazole Nitrate, USP, will not be altered and the excipients for the wax suppository portion of the proposed product will remain unchanged from the approved, non-encapsulated suppository. The material for use in manufacturing the gelatin shell is the same as that used to manufacture the approved Monistat 1.

The packaging is similar to the approved Monistat 3 packaging, but is identical to the packaging in use with the other currently approved and marketed Monistat vaginal antifungal products. In addition to minor revisions in the product specification due to use of a gelatin shell, a major change in the product specification is proposed by the inclusion of an *in vitro* dissolution test to serve as a quality control tool. The test method is well-described and satisfactorily validated. (b) (4)

attribute of this drug product.

Three commercial-sized batches of the proposed product were included in a stability study under both long-term (25°C/60% RH) and accelerated (40°C/75% RH) storage conditions. In addition to the tests listed in the specification, testing on (b) (4) (b) (4) was performed. The results from the first three months of these studies complied with the specification for product release and stability as well with the acceptance criteria for additional testing. Taken in their entirety these findings support the claim for product equivalency of the approved non-encapsulated and proposed encapsulated suppositories.

The stability commitment and protocol are acceptable. The stability studies will continue in order to confirm the proposed (b) (4) month expiry date. An overall recommendation of Acceptable for the (b) (4) facility in (b) (4) was made by OC on (b) (4) based on file review by the District. The (b) (4) facility in (b) (4) that will perform packaging and release testing underwent District inspection (completed on (b) (4)), but no final recommendation on the acceptability of this site has been made by OC as of 15-MAR-2007.

CONCLUSIONS & RECOMMENDATIONS:

The CMC information presented in the submission is sufficient to recommend APPROVAL of this supplement, pending OC approval of the (b) (4) facility in (b) (4).

cc: Orig. NDA 20-670
DMIHP/Division File
DMIHP/CSO/R.Hummel

filename: n20670s.014.doc

Allan Fenselau, Ph.D., Review Chemist

DRAFT SUPPLEMENT LETTER

There are no CMC-specific deficiencies, therefore no draft was generated.

Following this page, 15 pages withheld in full - (b)(4)

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

/s/

Allan Fenselau
3/15/2007 02:57:11 PM
CHEMIST

Hasmukh Patel
3/16/2007 02:22:56 PM
CHEMIST

The overall recommendation from the Office of Compliance is acceptable. Therefore, this supplement is recommended for APPROVAL action from the CMC standpoint.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-670 / S-014

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DIVISION OF McNEIL-PPC, INC.
199 Grandview Road
Skillman, New Jersey 08558

November 16, 2006

Via Courier

Charles Ganley, M.D., Director
US FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Non-Prescription Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prior Approval Supplement – Chemistry, Manufacturing and Controls

NDA 20-670: MONISTAT[®] 3 Combination Pack

[Miconazole Nitrate Vaginal Suppositories (200mg) and Miconazole Nitrate Cream (2%)]

Supplemental NDA Number 014

Dear Dr. Ganley,

Reference is made to the Personal Products Company (PPC) New Drug Application 20-670, MONISTAT[®] 3 Combination Pack, which was approved as an over-the-counter product by FDA on April 16, 2006 for the treatment of vulvovaginal candidiasis and the relief of associated external vulvar irritation. Reference is also made to the December 7, 2005 teleconference between PPC and USFDA, Office of Non-Prescription Products and the USFDA official meeting minutes dated December 20, 2005.

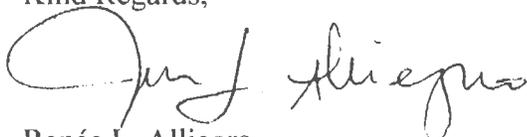
On behalf of PPC and in accordance with 21 CFR 314.70, please find enclosed a Chemistry, Manufacturing, and Controls (CMC) Prior Approval Supplement to support an alternate preparation of the Miconazole Nitrate Vaginal Suppository (200 mg), as currently approved and marketed under NDA 20-670. This alternate preparation is a gelatin-encapsulated vaginal suppository that will be made available as an alternative option to consumers in addition to the existing, approved MONISTAT[®] 3 Combination Pack.

Provided herein are three paper copies and one electronic copy of this submission. A field copy of this submission is being forwarded directly to the FDA offices in North Brunswick, New Jersey and (b) (4). We certify that the field copy is a true copy of the information contained in this supplemental application.

Ganley, Charles, M.D.
November 17, 2006
Page 2

The material and data herein are considered confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 USC, Section 331(j). Should you have any questions or concerns, please contact me directly via telephone at 908.904.3721 or via email at rkingall@cpcus.jnj.com.

Kind Regards,

A handwritten signature in black ink, appearing to read "Renée L. Alliegro". The signature is fluid and cursive, with a large initial "R" and "L".

Renée L. Alliegro
Manager, Regulatory Affairs
Johnson & Johnson Consumer and Personal Products Worldwide



DIVISION OF McNEIL-PPC, INC.
 199 Grandview Road
 Skillman, New Jersey 08558

ORIGINAL

CDER/CDR

DEC 11 2006

RECEIVED

Via Federal Express

December 07, 2006

Charles Ganley, M.D., Director
 US FOOD AND DRUG ADMINISTRATION
 Center for Drug Evaluation and Research
 Office of Non-Prescription Products
 5901-B Ammendale Road
 Beltsville, MD 20705-1266

RECEIVED

Sec 014(c)
 SUPPL NEW CORRESP

DEC 13 2006

OVER THE COUNTER

Submission of DMF Letter of Authorization to Accompany

Supplemental NDA Number 014

NDA 20-670: MONISTAT[®] 3 Combination Pack

[Miconazole Nitrate Vaginal Suppositories (200mg) and Miconazole Nitrate Cream (2%)]

Dear Dr. Ganley,

Reference is made to the Personal Products Company (PPC) New Drug Application 20-670, MONISTAT[®] 3 Combination Pack, which was approved as an over-the-counter product by FDA on April 16, 1996 for the treatment of vulvovaginal candidiasis and the relief of associated external vulvar irritation. Reference is also made to the Chemistry, Manufacturing, and Controls (CMC) Prior Approval Supplement (Supplemental NDA #014) to support an alternate preparation of the Miconazole Nitrate Vaginal Suppository (200 mg) that was submitted on behalf of PPC on November 17, 2006.

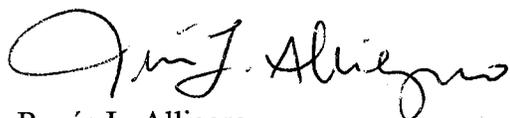
The number of the (b)(4) Drug Master File (DMF) was unavailable at the time of the submission, although a letter from (b)(4) was included as Appendix C on page 127 of the package. Since then, a DMF number has been assigned and (b)(4) has issued a new letter detailing the information about the DMF in connection with the PPC CMC Prior Approval Supplement that was submitted on November 17, 2006.

On behalf of PPC, please find enclosed the (b)(4) Letter of Authorization for DMF Number (b)(4). Provided herein are 3 copies of this submission. A field copy of this submission is being forwarded directly to the FDA offices in North Brunswick, New Jersey and (b)(4). We certify that the field copy is a true copy of the information contained in this supplemental application.

Ganley, Charles, M.D.
December 07, 2006
Page 2

The material and data herein are considered confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 USC, Section 331(j). Should you have any questions or concerns, please contact me directly via telephone at 908.904.3721 or via email at rkingall@cpcus.jnj.com.

Kind Regards,

A handwritten signature in black ink, appearing to read "Renée L. Alliegro". The signature is fluid and cursive, with a large initial "R" and "A".

Renée L. Alliegro
Manager, Regulatory Affairs
Johnson & Johnson Consumer and Personal Products Worldwide



NDA 20-670/S-014

PRIOR APPROVAL SUPPLEMENT

Personal Products Company
Division of McNeil
Attention: Renee L. Alliegro
Manager, Regulatory Affairs
199 Grandview Road
Skillman, NJ 08558

Dear Ms Alliegro:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Monistat 3-Combination Pack (200 mg, miconazole nitrate vaginal suppositories, 2%, miconazole nitrate cream)
NDA Number:	20-670
Supplement number:	014
Date of supplement:	November 16, 2006
Date of receipt:	November 17, 2006

This supplemental application proposes the following change(s): an alternate preparation of the vaginal suppository to the Chemistry, Manufacturing and Controls division; and labeling changes to the Consumer Information Leaflet.

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 16, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 15, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Drug Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-0941.

Sincerely,

{See appended electronic signature page}

Mary M. Lewis
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Drug Products
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/

Mary Lewis
2/16/2007 03:44:19 PM

FACSIMILE TRANSMISSION
RECORD



From: Allan Fenselau, Ph.D.

Office of New Drug Quality Assessment
Division of Post-Marketing Evaluation

Phone 301-796-1667

Fax 301-796-9748

Date: February 26, 2007

To: Name Ms. Renée L. Alliegro
Company Personal Products Company
City Skillman, NJ

Phone # 908-904-3721

FAX # 908-904-3480

e-Mail: rkingall@cpcus.jnj.com

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 796-1667 IMMEDIATELY if re-transmission is necessary.

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If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any view, disclosure, copying, or other action based on the content of this communication is NOT authorized. If you have received this document in error, please notify us immediately by telephone and return it to us at the above address by mail. Thank you.

Ms. Alliegro:

NDA 20-670/SCF-014

The following issues came up in reviewing the CMC component of your supplement SCF-014 to NDA 20-670 (MONISTAT® 3 Combination Pack). Please respond with an amendment to this supplement by 08-MAR-2007. Please let us know if this deadline cannot be met. If you have any questions about this matter or any other points in need of clarification, just call me (301-796-1667) or Robert Hummel (301-796-1981).

Thank you.

Allan Fenselau, Ph.D.
Review Chemist

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. 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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

NOTE: If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, please provide the appropriate information as an official amendment to the submission. In addition, a copy of your response submitted by e-mail or overnight delivery will expedite review of your request. In your cover letter refer to the date on which this information was requested.

Chemist's Concerns

1. Provide the file number for Drug Master File that describes the (b) (4) (b) (4) in the manufacture of the Miconazole Nitrate Vaginal Suppository (200 mg).

2. Correct the definition for (b) (4) suppository (see Footnote 1 in the table of product specifications on pp. 59-60).

3. Include greater detail on the (b) (4) test. Specifically,

(b) (4)

[In responding to this request, consider the ability of your test method to provide instructions that would permit an independent and qualified analyst to perform the testing successfully.] .

4. As presented, the (b) (4)

Justify the submitted (b) (4) .

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

/s/

Allan Fenselau
2/26/2007 11:24:34 AM
CHEMIST

Hasmukh Patel
2/26/2007 01:45:22 PM
CHEMIST



Personal Products
COMPANY

DIVISION OF McNEIL-PPC, INC.
199 Grandview Road
Skillman, New Jersey 08558

ORIGINAL

March 8, 2007

Via Federal Express

Charles Ganley, M.D., Director
US FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Non-Prescription Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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MAR 12 2007

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CDER White Oak DR1

MAR 09 2007

CDER CDR

Amendment to Prior Approval Supplement SNDA 014 – Chemistry, Manufacturing, and Controls
NDA 20-670: MONISTAT® 3 Combination Pack
[Miconazole Nitrate Vaginal Suppositories (200mg) and Miconazole Nitrate Cream (2%)]
Submission of Responses to FDA CMC Questions

SUPPLEMENT AMENDMENT

SCF-014 (BC)

Dear Dr. Ganley,

Reference is made to the Personal Products Company (PPC) New Drug Application 20-670, MONISTAT® 3 Combination Pack, which was approved as an over-the-counter products by FDA on April 16, 1996 for the treatment of vulvovaginal candidiasis and the relief of associated external vulvar irritation. Reference is also made to Supplemental NDA Number 014, a Chemistry, Manufacturing, and Controls (CMC) Prior Approval Supplement (PAS) dated November 16, 2006 submitted to FDA in support of an alternate preparation of the Miconazole Nitrate Vaginal suppository (200mg), as currently approved and marketed under NDA 20-670.

On behalf of PPC and in accordance with 21 CFR 314.70, please find enclosed an amendment to sNDA Number 014 containing the responses to CMC questions received from FDA via facsimile transmission on February 26, 2007. The material and data herein are considered confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 USC, Section 331(j). Should you have any questions or concerns, please contact me directly via telephone at 908.904.3721 or via email at rkingall@cpcus.jnj.com.

Kind Regards,


Renée L. Alliegro



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ONP**

FACSIMILE TRANSMITTAL SHEET

DATE: March 15, 2007

To: Barbara Popek, Regulatory Affairs For Renee L. Alliegro Manager, Regulatory Affairs	From: Mary Lewis Regulatory Project Manager
Company: Personal Products Company	Division of Nonprescription Clinical Evaluation
Fax number: 908-904-3748	Fax number: 301-796-9899
Phone number: 908-904-3708	Phone number: 301-796-0941
Subject: NDA 20-670/S-014; Monistat 3 (miconazole nitrate) Combination Pack; Prior Approval Supplement – Chemistry Supplement with Labeling	

Total no. of pages including cover: 4

Comments: We have reviewed your submission dated November 16, 2006 and have the following labeling comments. We request that you state your agreement to make these revisions and hand correct the label, labeling and consumer information leaflet along with initialing and dating each change. Please fax back to me by Friday morning, March 16, 2007.

Document to be mailed: YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2080. Thank you.

Attachment

FDA Labeling Comments:

I. Carton and Drug Facts Labeling

A. Principal Display Panel (PDP)

- The PDP is acceptable.

B. Drug Facts

1. Under *Directions*, remove the period from the first bulleted statement.
2. Under *Directions*, under the second bulleted statement, under the first sub-bullet, revise "**Vaginal Insert:**" to "**vaginal insert:**".
3. Under *Directions*, under the second bulleted statement, under the second sub-bullet, revise "**External Cream:**" to "**external cream:**".
4. Under *Directions*, under the second bulleted statement, under the first sub-bullet, revise "with a disposable applicator place the insert into the vagina." to "with a disposable applicator place the insert into the vagina at bedtime."
5. Under *Other information*, the Tamper-Evident Statement for the vaginal insert (first bulleted statement) was revised to read "do not use if printed sealed pouch containing vaginal insert is torn, open, or incompletely sealed". This is acceptable with two exceptions:
 - a. bold the word "printed" to be consistent with prior approved labeling.
 - b. revise the phrase "if printed sealed pouch containing vaginal insert is" to "if printed sealed pouches containing vaginal inserts are" to be consistent with the Tamper-Evident Warning on the carton bottom.
6. Under *Inactive ingredients*, the inactive ingredients for the vaginal insert should be in alphabetical order (e.g., move hydrogenated vegetable oil).

C. Fifth Panel

7. Delete the phrase [REDACTED]^{(b) (4)}, which is promotional.
8. Remove the words "[REDACTED]^{(b) (4)}". Effectiveness claims other than "Cures Most Vaginal Yeast Infections" have not been allowed in the past for any of the other OTC vaginal antifungal drug products.

D. Bottom Flap

9. Revise the statement "**TAMPER-EVIDENT UNIT DO NOT USE IF PRINTED SEALED POUCHES ARE TORN, OPEN, OR INCOMPLETELY SEALED**" by bolding the word "PRINTED" (unless the whole statement is bolded, which is acceptable).

II. Consumer Information Leaflet

10. Under "Why should I use MONISTAT® 3 Combination Pack?", underline the word "first" in the second bolded statement which reads: "*See your doctor or health professional first to find out the cause of your symptoms.*" to be consistent with prior approved labeling.
11. Under "What warnings should I know about when using MONISTAT® 3 Combination Pack", under "When using this product", add a fourth bulleted statement to read: "if you do not get complete relief ask a doctor before using another product", to be consistent with Drug Facts.
12. Under "Directions for using the applicator and 3 OVULE® Inserts", change the word "applicator" to "applicators".
13. Under "Directions for using the applicator and 3 OVULE® Inserts", in direction #7, add the sentence from prior approved labeling which reads: "This will reduce leakage." after the first sentence in direction #7 which reads "Lie down as soon as possible after inserting the OVULE® Insert."
14. Under "Other Information:"
 - a. The Tamper-Evident Statement was revised to read "TAMPER-EVIDENT UNIT - do not use if printed sealed pouch is torn, open or incompletely sealed. This is acceptable with one exception: change the words "pouch is" to "pouches are" to be consistent with carton labeling and Drug Facts.
 - b. Add the embossed design symbol to the second bulleted statement.
15. List the inactive ingredients in alphabetical order (e.g., relocate hydrogenated vegetable oil).

III. OVULE® Insert Pouch

- No changes needed. The OVULE® Insert pouch labeling is acceptable.

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this page is the manifestation of the electronic signature.**

/s/

Mary Lewis
3/15/2007 11:20:57 AM
CSO

Mary Lewis
3/15/2007 11:25:37 AM
CSO

Rec'd 3/16/07
M. Levin

Amendment to S-014



DIVISION OF McNEIL-PPC, INC.
199 Grandview Road
Skillman, New Jersey 08558

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MAR 16 2007

CDER White Oak DR 1

March 16, 2007

Charles Ganley, M.D., Director
US FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Non-Prescription Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 20-670/S-014 Monistat 3 (miconazole nitrate) Combination Pack; Prior Approval Supplement - Chemistry Supplement with Labeling

SUPPLEMENT AMENDMENT

SCF-014(BL)

Dear Mary Lewis:

Reference is made to the fax from FDA dated March 15, 2007. We are in agreement of all the labeling corrections as outlined. Attached is a copy of the original submission for the carton and consumer information leaflet with the corrections noted, initialed and dated.

Reference is also made to PPC's fax of March 16, 2007 and our subsequent discussion regarding our proposal of (b)(4) on the fifth panel of the carton. We agree to delete (b)(4). The statement will read "3 Day OVULE Insert Treatment". Attached is a copy of the front panel indicating that change.

Please let me know if there are any other concerns. I look forward to receiving the approval letter later on today.

Sincerely,

Barbara Popek
Manager, Regulatory Affairs



DIVISION OF McNEIL-PPC, INC.
199 Grandview Road
Skillman, New Jersey 08558

August 10, 2007

Charles J. Ganley, M.D. Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products (HFD-560)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 20-670
MONISTAT 3[®] Combination Pack
FPL for Supplement NDA 20-670/S-014

Dear Dr. Ganley:

Reference is made to Personal Products Company's (PPC) New Drug Application 20-670 and Supplement S-014, approved March 16, 2007 for MONISTAT[®] 3 Combination Pack.

Accordingly, enclosed please find a CD ROM containing the final printed labeling (FPL), as follows:

- MONISTAT[®] 3 Combination Pack – Carton Label
- MONISTAT[®] 3 Combination Pack – Consumer Information Leaflet
- MONISTAT[®] 3 Combination Pack – Pouch Label

We trust that this FPL is acceptable and respectfully request that this submission be made part of the subject NDA.

Should you have comments or questions please contact Dina Russello directly at 973-385-4909.

Respectfully submitted,

Renee L. Alliegro
Manager, Regulatory Affairs

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AUG 14 2007

CDER/WHITE OAK/DRI

RECEIVED

AUG 13 2007

CDER COR

NDA SUPPL AMENDMENT

SCF-014-FA
ORIGINAL

(b) (4)

ARTWORK SPECIFICS

(b) (4)

