CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-261

CORRESPONDENCE

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

January 29, 2001

Dr. Charles Ganley, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products
Attn: Document Control Room
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-261
MONISTAT® 3 Cream Combination Pack
NDA Commitment Letter - Revised

Dear Dr. Ganley:

Reference is made to our NDA commitment letter dated January 25, 2001 in which we agreed to add the statement "**Ask a doctor or pharmacist before use if you are** taking a prescription blood thinning medicine, such as warfarin." to our drug facts box on the product carton. At this time we are revising the statement as per our conference call with FDA on January 29, 2001 to read "**Ask a doctor or pharmacist before use if you are** taking the prescription blood thinning medicine warfarin, because bleeding or bruising may occur."

Personal Products Company (PPC) will commit to specifying that the draft labeling dated January 4, 2001, with the revisions in our letter dated January 25, 2001 and the revision listed above, will serve as the approved labeling for NDA 21-261.

In addition, PPC will commit to providing our 1-800 phone number with information to address questions in reference to the warfarin warning, train our detailing sales force to respond to this question when asked and include the warfarin statement as it is in our labeling on our next Physician/Pharmacist Detail piece.

If there are any questions regarding this commitment, please contact me at (908) 904-3708.

Sincerely,

Barbara Popek
Manager, Regulatory Affairs

cc: Daniel Keravich, Project Manager, DOTCDP (HFD-560)
Linda Katz, Supervisory Medical Officer, DOTCDP (HFD-560)

Personal Products
COMPANY

DIVISION OF McNEIL-PPC, INC.
199 GRANDVIEW ROAD
SKILLMAN, NJ 08558

January 25, 2001

Dr. Charles Ganley, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)
Attn: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-261
MONISTAT® 3 Cream Combination Pack
NDA Commitment Letter

Dear Dr. Ganley:

Reference is made to the fax from the FDA dated January 24, 2001 regarding the draft labeling for NDA 21-261 MONISTAT 3 Cream Combination Pack.

Personal Products Company (PPC) will commit to specifying that the draft labeling dated January 4, 2001, with the revisions specified below, will serve as the approved labeling for NDA 21-261. Those revisions are:

1. Carton Label:
   a. Remove the word "New" in the phrase "New Combo Pack!" after the first 6 months of OTC marketing.
   b. Change the PDP so that the declaration of net quantity of contents clearly indicates that the statement refers to 2 products. We will either separate the two phrases with the word "and" or place each phrase on a separate line.
   c. The Warning in the Drug Facts box will be revised to read "**Ask a doctor or pharmacist before use if you are** taking a prescription blood thinning medicine, such as warfarin."
2. Consumer Information Leaflet:
   a. Revise the heading "**Use**" to "**Uses**".
   b. In the **Warnings** section, revise the 5th bulleted warning to read: "Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine warfarin (coumadin), because bleeding and bruising may occur."

c. Under the heading "**Side effects**" revise the third sentence to read "Stop using MONISTAT® 3 Vaginal Cream Combination Pack and consult your doctor if you have abdominal pain, hives, or skin rash, or if you have severe vaginal burning, itching, or irritation."
d. In the 4th direction, first sentence, under the heading "**Directions for Use MONISTAT® 3 Vaginal Cream,**" we will add the word "back" as follows; "Gently insert the applicator into the vagina as far back as it will go comfortably."

We acknowledge that the agency agrees to allow PPC to use the current tube and current overwrap labeling for the product launch. We do commit to incorporating the new labeling within 180 days or at the next printing. We also acknowledge that the agency agrees that the use of a picture of a hand (instead of an arrow) to show where the applicator is inserted is acceptable.

If there are any questions regarding this commitment, please contact me at (908) 904-3708.

Sincerely,

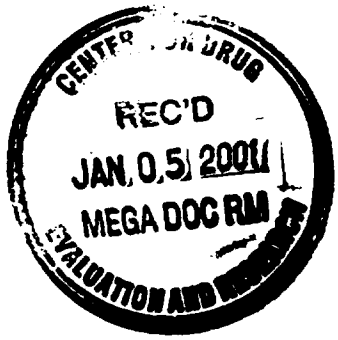
Barbara Popek

Barbara Popek
Manager, Regulatory Affairs
Personal Products Company

Cc: Daniel Keravich, Project Manager, DOTCDP (HFD-560)

Personal Products
COMPANY

DIVISION OF McNEIL-PPC, INC.
199 GRANDVIEW ROAD
SKILLMAN, NJ 08558



January 4, 2001

Dr. Charles Ganley, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)
Attn: Division Document Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA 21-261
MONISTAT® 3 Cream Combination Pack
NDA AMENDMENT – REVISED DRAFT LABELING

Dear Dr. Ganley:

Reference is made to the faxes sent by the FDA to PERSONAL PRODUCTS COMPANY (PPC) dated December 1 and December 27, 2000. These communications provided PPC with the reviewer's comments on the labeling submitted to pending NDA 21-261, MONISTAT® 3 Cream Combination Pack. At this time, PPC would like to amend NDA 21-261 to provide revised draft labeling for the carton, consumer information leaflet, 9 gram tube (external vulvar cream) and prefilled applicator overwrap.

In the original submission, PPC noted that the labeling for the applicator overwrap and the 9 gram external cream tube were identical to the labeling that had been previously approved under NDAs 17-450, 20-827, 20-288, 20-670 and 20-968. These components were not going to be produced especially for this product, but co-packaged. In that submission, PPC requested permission to use these existing components for the launch this product. Since the changes to the 9 gram tube and overwrap, requested by the reviewer, are major and to minimize complexity at the manufacturing site, PPC is requesting permission to use the currently available tube and overwrap components for the launch of this product.

If permission is granted, based on current tube and overwrap inventory we would commit to incorporating the new tube and overwrap labeling for this NDA within 180 days of approval or at the next printing. In order to keep all components consistent and to avoid consumer confusion, we will also commit to making the same tube and overwrap changes for NDAs 17-540, 20-827, 20-288, 20-670, and 20-968 by August 2001. (We also requested to use the current 9 gram tube in the

pending Rx to OTC switch NDA 21-308 MONISTAT 1 Combination Pack. For consistency purposes, we will also file a label amendment for the 9 gram tube to that NDA.)

Please contact me directly with any questions you may have related to this submission. I can be reached at (908) 904-3708 and via fax at (908) 904- 3748.

Sincerely,

Barbara Popek

Barbara Popek
Manager, Regulatory Affairs
PERSONAL PRODUCTS COMPANY

Cc: Daniel Keravich, Project Manager (HFD-560)

Personal Products
COMPANY

199 Grandview Road
Skillman, New Jersey 08558

September 11, 2000

Mr. Daniel Keravich
Division of Over-the-Counter Drug Products (HFD-560)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-261 MONISTAT® 3 (miconazole nitrate) Cream Combination Pack

Dear Mr. Keravich:

In response to your request of August 30, 2000, enclosed, please find a diskette containing electronic Principal Display Panels (PDPs) of our current MONISTAT® 3 products along with our proposed PDP for the subject NDA, MONISTAT 3 Cream Combination Pack. The PDPs for our current products have been updated to modify the Statement of Identity to be consistent across the brand. These modifications are scheduled for implementation in 2001.

The enclosed diskette contains five documents in PDF format (Adobe). At this time, we are unable to provide these PDPs in Word or PowerPoint format unless they are imbedded PDF files. The file names and descriptions are as follows:

File Name	Description
[redacted]	MONISTAT 3 Combination Pack
	MONISTAT 3 Combination Pack w/Disposable Applicators
	MONISTAT 3 Cream Combination Pack –PROPOSED-
	MONISTAT 3 Vaginal Cream w/Disposable Applicators
	MONISTAT 3 Vaginal Cream in Prefilled Applicators

Should you need additional information, please contact the undersigned directly.

Sincerely,
PERSONAL PRODUCTS COMPANY

Lynn A. Pawelski
Director, Regulatory Affairs

Personal Products
COMPANY

199 Grandview Road
Skillman, New Jersey 08558

September 7, 2000

Charles Ganley, M.D.
Director,
Division of Over-the-Counter Drug Products (HFD-560)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

RE: **NDA 17-450 MONISTAT® 7 (miconazole nitrate 2%)Vaginal Cream**
NDA 18-520 MONISTAT® 7 (miconazole nitrate, 100mg) Vaginal Suppositories
NDA 20-288 MONISTAT® 7 (miconazole nitrate) Combination Pack
NDA 20-670 MONISTAT® 3 (miconazole nitrate) Combination Pack
NDA 20-827 MONISTAT® 3 (miconazole nitrate cream) Vaginal Cream
NDA 21-261 MONISTAT® 3 (miconazole nitrate) Cream Combination Pack

Dear Dr. Ganley:

This letter serves to inform you of a name change, new address and contact information for the above referenced NDAs. Advanced Care Products (ACP) has been an operating unit within Personal Products Company, A Division of Mc-Neil-PPC. At this time, Advanced Care Products will no longer be used and we will only be referred to as Personal Products Company (PPC). There is no change in management structure associated with this change.

At this time we are also relocating from 691 Highway 1 South, North Brunswick, New Jersey to our headquarters facility. Official contact persons and associated information regarding this move follows. The move is effective Monday, September 11, 2000.

Primary Contact:
Lynn A. Pawelski (SF 409)
Director, Regulatory Affairs
Personal Products Company
199 Grandview Road
Skillman, NJ 08558

Phone: (908) 874-3745
Fax: (908) 874-3746

Secondary Contact:
Barbara Popek (SF 108)
Manager, Regulatory Affairs
Personal Products Company
199 Grandview Road
Skillman, NJ 08558

Phone: (908) 874-3708
Fax: (908) 874-3746

Should you need additional information, please contact the undersigned directly.

Sincerely,
PERSONAL PRODUCTS COMPANY

Lynn A. Pawelski
Director, Regulatory Affairs

cc: Daniel Keravich

Advanced Care Products
Personal Products Company
691 Highway 1
P.O. Box 6024
North Brunswick, NJ 08902-0724

August 29, 2000

Dr. Charles Ganley
Director, Division of Over-the-
Counter Drug Products, HFD-560
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

REQUEST FOR TELECONFERENCE
NDA 21-161
MONISTAT 3 CREAM COMBINATION PACK
Miconazole Nitrate 4% Vaginal Cream (200 mg per applicator) and 2% External Cream

Dear Dr. Ganley:

Reference is made to NDA 21-261 for the MONISTAT 3 Vaginal Cream submitted on March 31, 2000. Reference is also made to the August 25, 2000 fax from the agency regarding concerns with the proposed name of the subject product. At this time, Advanced Care Products, Personal Products Company is requesting to meet with the agency to discuss the issues raised. A list of questions we are posing to the review team is attached.

We look forward to securing a meeting date to discuss and hopefully reach a resolution on these issues as soon as possible and will make ourselves available at any time that is convenient for the review team.

If you have any questions, please feel free to contact the undersigned at (732) 524-1515 or in my absence, Barbara Popek at (732) 524-1372.

Sincerely,

Lynn A Pawelski

Lynn Pawelski
Director, Regulatory Affairs

Enclosure: Questions for Review Team

cc: Daniel Keravich, Project Manager, DOTCDP (HFD-560)
Christina Chi, Project Manager, DSPIDP (HFD-590)

QUESTIONS FOR REVIEW TEAM

1) The review team has raised a concern over the possibility of consumer confusion with the use of the name "MONISTAT® 3 Cream combination pack". If there were consumer confusion, what are the possible negative outcomes?

2) MONISTAT has historically been the trade name associated with the ingredient miconazole nitrate, does the agency believe that this association is a cause of confusion for the consumer?

3) Does the review team have concern with the use of the trade name "MONISTAT" on the proposed product?

4) In the category of products for vaginal treatment of vulvovaginal candidiasis, FDA has historically approved these products with name designations including a number (referring to days of treatment), does the agency believe that this practice confuses the consumer?

5) Does the review team agree that the treatment of the yeast infection is a 3 day treatment?

   a) If yes, does the agency believe that the inclusion of the number three is appropriate? Why (or why not)?
   b) If no, is it because the agency believes that the external cream is a treatment (i.e., cure) instead of a symptom reliever to be used as needed?

6) Does the review team have concern with the use of the number "3" to refer to the length of treatment?

7) What specific concerns, other than those which may have already been addressed, does the agency have related to the referenced potential consumer confusion? While there are multiple products which contain "MONISTAT 3" and "COMBINATION PACK" in their labeling, these two phrases never occur in succession or without intervening text explaining the identity of the ingredient and the product form. This information in fact appears in two places on the principal display panel and in a visual on the 5th panel.

   Is there an opportunity to revise how the ingredient and product form are labeled in order to address the agency's concerns?

Personal Products
COMPANY

DIVISION OF McNEIL-PPC, INC.
691 HIG HWAY 1 SOUTH
P.O. BOX 6024
NORTH BRUNSWICK, NJ 08902-6024

8/29/00

August 25, 2000

Dr. Charles Ganley
Director, Division of Over-the-Ccunter Drug Products (HFD-560)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockvillle, MD 20850

AMENDMENT
SU

SUBJECT: NDA 21-261
Clinical Amendment

Dear Dr. Ganley,

Reference is made to teleconferences on August 23 and 24, 2000. FDA has requested that Personal Products Company (PPC) provide copies of all the referenced safety update submissions listed in the original NDA submission.

Included herein is a copy of the following:

1. NDA 20-827- QUARTERLY REPORT, March 1, 2000-May 31, 2000; submitted June 29, 2000 (additional data)
2. NDA 20-827- QUARTERLY REPORT, December 1, 1999-February 29, 2000; submitted March 23, 2000
3. NDA 20-827- QUARTERLY REPORT, September 1, 1999-November 30, 1999; submitted December 21, 2000
4. NDA 20-827- QUARTERLY REPORT, June 1, 1999-August 31, 1999; submitted November 5, 1999
5. NDA 20-827- QUARTERLY REPORT, March 1, 1999-May 31, 1999; submitted July, 1, 1999
6. NDA 20-827- QUARTERLY REPORT, December 1, 1998-February 28, 1999; submitted April 1, 1999
7. NDA 17-450 – PERIODIC ANNUAL REPORT, January 1, 1999-December 31, 1999; Submitted February 21, 2000

ORIGINAL

Each report contains the original summary, Medwatch forms organized by adverse event, all "ineffective" forms have been eliminated, as requested.

Please contact me directly with any questions you may have related to this submission. I can be reached at (732) 524-1515 and via fax at (732) 524-1344

Sincerely,
PERSONAL PRODUCTS COMPANY

Barbara Popek
for Lynn Pawelski
Director, Regulatory Affairs

cc. Daniel Keravich, Project Manager (HFD-560)

Personal Products

March 31, 2000

Dr. Charles Ganley
Director, Division of
Over-the-Counter Drug Products (HFD-560)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

SUBJECT: ORIGINAL NDA 21-261
MONISTAT® 3 Cream Combination Pack

Dear Dr. Ganley:

Reference is made to approved NDA 17-450 for MONISTAT® 7 Vaginal Cream as well as to NDA 20-827 for MONISTAT 3 Vaginal Cream. Reference is also made to submissions of January 27 and February 24, 2000 and to teleconferences on March 27 and March 31, 2000. At this time Personal Products Company (PPC) is requesting approval to market a new 3-day combination pack. The proposed product, MONISTAT® 3 Cream Combination Pack would consist of miconazole nitrate 4% cream (200 mg per applicator) and a 9 g tube of miconazole nitrate 2% external cream.

As agreed upon in our teleconference of March 31, 2000, we are submitting an original New Drug Application at this time. While the application is eligible for submission as an efficacy supplement, we are submitting it as a new NDA for the administrative convenience of the FDA review division.

Included herein is a copy of the proposed labeling for the new product as well as a safety update. You will note that the claims for each component (vaginal cream in prefilled applicators and external cream) are consistent with the claims approved in their subject NDAs.

Please contact me directly with any questions you may have related to this submission. I can be reached at (732) 524-1515 and via fax at (732) 524-1344.

Sincerely,
PERSONAL PRODUCTS COMPANY

Lynn A. Pawelski

Lynn Pawelski
Associate Director, Regulatory Affairs

cc: Daniel Keravich, Project Manager (HFD-560)

Advanced Care Products
Personal Products Company
691 Highway 1
P.O. Box 6024
North Brunswick, NJ 08902-0724

OTC# 00-302

January 27, 2000

Dr. Mark Goldberger
Director, Division of Special Pathogens and
Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

Dr. Charles Ganley
Director, Division of Over-the-
Counter Drug Products, HFD-560
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

REQUEST FOR MEETING
Proposed MONISTAT 3 CREAM COMBINATION PACK
Miconazole Nitrate 4% Vaginal Cream (200 mg per applicator) and 2% External Cream

Dear Drs. Goldberger and Ganley:

Reference is made to approved NDA 20-827 for the MONISTAT 3 Vaginal Cream (miconazole nitrate 4% - 200 mg per applicator) approved on March 30, 1998. Reference is also made to approved NDAs 20-288 and 20-670 for MONISTAT 7 and 3 Combination Packs, respectively. At this time, Advanced Care Products (ACP) is requesting to meet with the agency to discuss a proposed new Combination Pack, MONISTAT 3 Cream Combination Pack. This proposed product would consist of miconazole nitrate 4% vaginal cream (200 mg per applicator) and miconazole nitrate 2% external cream.

This combination pack is intended to provide consumers with an option for additional external relief while using the miconazole nitrate 4% cream vaginally. This is being proposed since the 2% cream has long been approved for external use and is a component of other approved vaginal/topical combination products, including MONISTAT 3 Combination Pack. The currently approved MONISTAT 3 Combination Pack (200 mg suppositories and 2% external cream) consists of the same level of drug (200 mg miconazole nitrate administered vaginally) and route of administration as is part of this proposal. It is important to note that it is not, nor has it ever been hypothesized that the 2% cream in any way affects the overall cure of the yeast infection. It (2% external cream) is being proposed for inclusion as it is desired by consumers to provide them with relief of their external symptoms while waiting for the vaginal component to cure their infection.

Included in this meeting request, please find a background document which we believes supports the rationale for this combination product. Also included is the list of questions we wish to discuss at the meeting as well as a list of proposed attendees.

If you have any questions, please feel free to contact me at (732)-524-1515. We look forward to meeting with you to discuss this proposed packaging configuration as soon as possible.

Sincerely,

Lynn A. Pawelski

Lynn Pawelski
Associate Director,
Regulatory Affairs

Enclosure: List of Attendees
Questions to be Discussed
Background Materials

cc: Christina Chi, Project Manager, DSPIDP (HFD-590)
Daniel Keravich, Project Manager, DOTCDP (HFD-560)

LIST OF ATTENDEES

Advanced Care Products, Personal Products Company

Lynn Pawelski, Associate Director, Regulatory Affairs
David Upmalis, Executive Director, Clinical Affairs

Division of Over-The-Counter Drug Products

As required

Division of Special Pathogen and Immunologic Drug Products

As required

APPEARS THIS WAY
ON ORIGINAL

LIST OF QUESTIONS/ISSSUES TO BE DISCUSSED

1. The Division of Special Pathogens and Immunologic Drug Products (DSPIDP) has informed us that this type of application will require a re-review of the clinical data submitted in the original New Drug Application 20-827 for MONISTAT® 3 Vaginal Cream (miconazole nitrate 4% cream). Since that product was recently approved (3/98), we do not understand the objective of this requirement or what information is to be derived from such a review. We especially doubt that such a review would provide additional key information beyond what was available under the first review. We wish for the agency to clarify this requirement and specify what the goals of such a review would be.

2. If a re-review of the clinical data in NDA 20-827 is required, it will not be new clinical data and should not be subject to a user fee. We request the agency clarify the user fee requirements of a supplement of the type proposed (no new clinical data). We also wish to discuss the type of application which should be filed to support the proposal (supplemental application, new NDA) and the associated user fee requirements.

3. It is proposed that the 2% external cream with its emollient cream base be included to provide for external symptom relief only. The agency has already concurred this is an appropriate indication for the 2% cream (approved for use an as external vulvar cream to provide relief of external itching and irritation associated with a vaginal yeast infection in MONISTAT® 3 and 7 Combination Packs, MONISTAT® 7 Cream and the MONISTAT® DUAL-PAK); does the agency feel that its benefit/safety profile would support its inclusion in the proposed product?

4. It is our position that the proposed product (miconazole nitrate 4% vaginal cream (200 mg per applicator) and miconazole nitrate 2% external cream) is identical to an already approved combination with the same dosages and routes of administration (MONISTAT 3 Combination Pack; miconazole nitrate 200 mg vaginal suppositories and 2% external cream). Does the agency concur with this assertion?

5. Since the proposed new product is not a new combination, but is a new form of an already approved combination, we are not planning to conduct trials supporting this proposed combination. It is not expected that new trials would offer any additional information other than to support that the 2% external cream provides external symptom relief. Since there is already a wealth of data to support this external relief claim for the 2% cream, clinical studies would be redundant and unproductive. Does the agency concur?

If the agency does not concur on Questions 1-5, we would request the agency respond to the following questions.

1. It is not our position that the 2% external cream contributes to a better cure (or a higher rate of cure) than the vaginal components (200 mg miconazole nitrate cream in this case). This equivalence of vaginal treatment alone to vaginal treatment plus external symptoms relief has also been shown in clinical trials to support NDA 20-670. Therefore, it is not appropriate to apply a traditional combination policy (requiring clinical studies to show that the combination is better than the components alone) as this will not show a differentiation between the two types of products. Does the agency concur?

2. If the agency believes that the proposed product is a new combination, we would like to have the agency review the type of information that would be required to support the product's over-the-counter availability.

Proposed MONISTAT® 3 Cream Combination Pack

BACKGROUND INFORMATION

At this time, Advanced Care Products (ACP) is proposing to market a new combination pack which will include a 200 mg/dose miconazole nitrate cream (approved via NDA 20-827) either in prefilled or reusable applicators and a 2% miconazole nitrate external cream. This proposal is based primarily on the equivalence of the 200 mg cream and suppository formulations.

While the equivalence of the 200 mg vaginal cream and 200 mg vaginal suppository formulations has not been proven in a direct study comparing the two, both have been deemed equivalent to MONISTAT® 7 Vaginal Cream in studies required for OTC availability. It would therefore be reasonably expected that their actions would be similar and therefore that the two could be used interchangeably to treat a vaginal yeast infection.

With regard to the use of the 2% external cream in addition to the 200 mg Vaginal Cream, it has long been shown that consumers do have a preference for an external treatment (symptom relief) in addition to the internally applied treatment. It is for this reason that we are proposing to offer this combination pack to consumers. Miconazole nitrate 2% external cream has already been approved for use with a 200 mg vaginal treatment in the subject NDA.

It also follows that the 2% cream is a reasonable addition to the vaginal therapy in that it has already been shown to be safe to use topically in OTC drug products via approved NDAs 20-288 and 20-670. It was also generally recognized as safe and subsequently included in the antifungal monograph.

The addition of the miconazole nitrate 2% external cream to the already approved 200 mg vaginal cream product will not affect the efficacy profile of the vaginal cream. It has been shown in multiple studies of over-the-counter miconazole nitrate combination products that the addition of the 2% external cream does not affect either the safety or efficacy profile of the vaginal treatment. That is, the combination of the two components has not shown a significant treatment benefit over vaginal therapy alone, but it has been proven equivalent to vaginal therapy alone and has also shown a great consumer benefit in providing external symptom relief.

In summary, since the combination of a 200 mg miconazole nitrate vaginal therapy and 2% miconazole nitrate external cream is already an approved and efficacious product combination, we are proposing a new packaging configuration consisting of miconazole nitrate 200 mg Vaginal Cream and 2% external cream. The safety of this combination will be further discussed in the clinical/safety rationale included herein.

Proposed MONISTAT® 3 Cream Combination Pack

BACKGROUND INFORMATION

INTRODUCTION

The high efficacy rate and exceptional safety of miconazole nitrate 2% external cream supports its use for external symptom relief in the MONISTAT line of products. At this time we are proposing that this 2% external cream be combined with the 200 mg 3-day vaginal cream to also give patients relief of external symptoms. This is being proposed with the 2% cream as the 3-day, 4% miconazole nitrate cream has not been tested with relation to its ability to relief external vulvar symptoms, while this has been well-established for the 2% miconazole nitrate cream.

This use will not mask symptoms of other conditions, so the benefit/risk balance is still favorable. It has the added benefit as a better alternative than symptom-relief home remedies or external analgesic products used to relieve the external symptoms of a vaginal yeast infection as those remedies cannot aid in cure the infection and may increase skin irritation in some instances.

In conclusion there is no potential for harmful effects with the addition of 2% miconazole nitrate external cream to the MONISTAT® 3 200 mg per dose cream already approved for internal use. It offers only added benefits (symptom relief) with no additional risks.

CLINICAL RATIONALE

It is intuitive that the application of an emollient topical cream to an inflamed, irritated vaginal and vulvar epithelium will provide temporary symptomatic relief in women who have vulvovaginal candidiasis (VVC). This was the rationale that led to the approval and subsequent marketing of the Monistat vaginal therapies (Monistat 7 Vaginal Suppositories and Monistat 3 Vaginal Suppositories) with topical miconazole nitrate 2% cream. This cream has already been approved for topical application, indicated for the treatment of tinea pedis and tinea corporis and also for the relief of accompanying symptoms. It therefore was logical to extend the relief indication to include the relief of external symptoms associated with VVC. By using a cream containing the active ingredient found in the vaginal therapy, no concerns regarding a potential dilution effect would be aroused. Thus, efficacy would not be compromised. Additionally, any external involvement in the infection could be treated. Since the 2% topical formulation is in widespread use, no safety issues were evident.

The current proposal is for the addition of a tube of topical 2% miconazole nitrate cream (Monistat External Vulvar Cream) to Monistat 3 Vaginal Cream. This is felt appropriate both from a medical perspective as well as a consumer perspective. For the consumer, the provision of a local treatment that temporarily relieves the symptoms associated with VVC is highly attractive. Clinical trials of Monistat products in "Dual-Pak" formulations have shown that, on average, 75% of women in these trials elect to use the topical cream. Comparison of sales figures for Monistat 7 Combination Pack and Monistat 7 Vaginal

Proposed MONISTAT® 3 Cream Combination Pack

BACKGROUND INFORMATION

Suppositories, (Table 1) demonstrate, again, this preference in more recent years. From a medical perspective, it has been a longstanding practice for medical practitioners to advise patients, when prescribing vaginal creams for VVC to take a small amount from the tube of vaginal cream and apply it to the vulva for symptomatic relief. Thus, the pattern of practice is well established, both for combination packs and for the medical practice of applying vaginal antifungal cream topically.

Data are provided to document that the use of miconazole nitrate 2% topical cream has not led to an increase in adverse experiences. Table 1 (below) documents the total number of adverse experiences for both Monistat 7 Combination Pack, providing 7x100 mg miconazole nitrate vaginal suppositories and a 9 gm tube of miconazole nitrate cream for external application. It is evident that the adverse experience rate for both products is remarkably low. Thus, the provision of and, presumably, use of the topical cream over a number of years of extensive use with easy access to a consumer complaint line, has not documented any safety issue arising from the provision of miconazole nitrate 2% cream with the Monistat 7 Vaginal Suppositories.

Table 1: Comparison of complaints for Monistat 7 Combination Pack and Monistat 7 Vaginal Suppositories

Year	*Monistat 7 Combination Pack*			*Monistat 7 Vaginal Suppositories*		
	Sales	**# of AEs**	**AEs/1000 units sold**	**Sales**	**# of AEs**	**AEs/1000 units sold**
1996		89			87	
1997		61			42	
1998		124			51	
1999 (to date)		66			29	

To date, no similar situation exists for Monistat 3 products. The products currently on the market are a Monistat 3 Combination Pack that provides three doses of 200 mg suppository with 9 gm of Monistat External Vulvar Cream and Monistat 3 Vaginal Cream, delivering three doses of 5 gm of 4% miconazole nitrate in a cream form. Comparison of adverse experience rates for the two products are shown in Table 2. It is appears that the adverse experience rate is appreciably lower for the combination pack compared to Monistat 3 Vaginal Cream (note that the rates are still acceptably low). This may be due to the most recent introduction of Monistat 3 Vaginal Cream, since, invariably, new product introductions in the marketplace are found to incur high complaint rates through the 800 number.

Proposed MONISTAT® 3 Cream Combination Pack

BACKGROUND INFORMATION

Table 2: Comparison of Adverse Experiences for Monistat 3 Combination Pack and Monistat 3 Vaginal Cream

Year	*Monistat 3 Combination Pack*			*Monistat 3 Vaginal Cream*		
	Sales	**# of AEs**	**AEs/1000 Units Sold**	**Sales**	**# of AEs**	**AEs /1000 units sold**
1996		575				
1997		620				
1998		494			332	
1999(to date)		181			419	

In summary, miconazole nitrate 2% cream is broadly available for topical applications, indicated to treat superficial fungal infections as well as to relieve the symptoms associated with such infections. Extensive experience with miconazole nitrate 2% cream for the temporary symptomatic relief of external symptoms associated with vaginal yeast infections shows that there is no added risk in supplying this cream, while there is some benefit. As mentioned, physicians often recommend their patients apply a small amount of cream taken from vaginal application to apply external specifically to relieve their symptoms. It is entirely possible that consumers are following this practice currently with Monistat 3 Vaginal Cream – a 4% miconazole nitrate cream. The provision of a separate tube of 2% miconazole nitrate topical cream for external symptoms would be preferred to such a practice, as a lower concentration of miconazole nitrate would be used, possibly reducing the irritation that may be attributable to miconazole nitrate.

NDA 21-261

Personal Products
Attention: Lynn Pawelski
691 Route 1 South
P.O. Box 6024
North Brunswick, New Jersey 08902

Dear Mrs. Pawelski:

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

Name of Drug Products: Monistat 3 Cream Combination Pack (miconazole nitrate) internal and external creams

Therapeutic Classification: Standard (S)

Date of Application: March 31, 2000

Date of Receipt: April 3, 2000

Our Reference Number: NDA 21-261

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 2, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 3, 2001 and the secondary user fee goal date will be April 3, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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

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

NUMBER
5600 Fishers Lane
Rockville, Maryland 20857

NUMBER
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Daniel P. Keravich, M.S., M.B.A., Regulatory Health Project Manager, at -2748.

Sincerely,

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 21-261
HFD-560/Div. Files
HFD-560/D.Keravich
HFD-560/Ganley/Katz/Chinl/Cothran/Turner/Cook
HFD-590/Chi/Albrecht/Leissa/Matecka/Frank

DISTRICT OFFICE

Drafted by: dpk/April 12, 2000
Initialed by:
final:

ACKNOWLEDGEMENT (AC)