

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-308

ADMINISTRATIVE DOCUMENTS

NDA 21-308
MONISTAT[®] 1 Combination Pack
(miconazole nitrate 1200mg Soft Gel Vaginal Insert and 2% external vulvar cream)
ITEM 13: PATENT INFORMATION

As per 21 CFR§314.53, we hereby submit the following patent information:

- (i) Patent Number: 6,153,635
Date of Patent Expiration: November 28, 2020
- (ii) Type of Patent: Drug Product
- (iii) Patent Owner: McNeil-PPC, Inc.
Skillman, New Jersey 08558
- (iv) Patent Owner does not have a place of business in the United States.

The undersigned declares that Patent No. 6,153,635 covers the formulation and composition of the miconazole nitrate 1200 mg soft gel vaginal insert and the 2% external vulvar cream. These two products together are the subject of this application for which OTC approval is being sought.



US006153635A

United States Patent [19]
Upmalis

[11] **Patent Number:** **6,153,635**
[45] **Date of Patent:** **Nov. 28, 2000**

[54] **METHODS AND KITS FOR TREATING
VULVOVAGINAL CANDIDIASIS WITH
MICONAZOLE NITRATE**

Primary Examiner—Theodore J. Criares
Attorney, Agent, or Firm—Reed Smith Shaw & McClay
LLP

[76] **Inventor:** **David H. Upmalis**, 51 Declaration Dr.,
Newtown, Pa. 18940

[57] **ABSTRACT**

[21] **Appl. No.:** **09/197,019**

A method for treating vulvovaginal candidiasis including the steps of: (a) administering a single dose of an effective amount of miconazole nitrate in a pharmaceutically acceptable carrier intra-vaginally; and (b) applying miconazole nitrate in a pharmaceutically acceptable carrier to the vulva. Also a kit for the treatment of vulvovaginal candidiasis including: (a) a single dose of an effective amount of miconazole nitrate in a pharmaceutically acceptable carrier and in a form adapted to be administered intra-vaginally; and (b) an amount of miconazole nitrate in a pharmaceutically acceptable carrier adapted to be applied topically to the vulva.

[22] **Filed:** **Nov. 20, 1998**

[51] **Int. Cl.**⁷ **A61K 31/415**

[52] **U.S. Cl.** **514/399; 514/931**

[58] **Field of Search** **514/399, 931**

[56] **References Cited**

PUBLICATIONS

Olin, B.R. et al., *Facts and Comparisons*, St. Louis, MO: JB Lippincott Co. (Oct. 1985) pp. 355a-355b.
Olin, B.R. et al., *Facts and Comparisons*, St. Louis, MO: J.B. Lippincott Co. (Nov. 1989), pp. 528-530.

13 Claims, No Drawings

ORIGINAL NEW DRUG APPLICATION
NDA 21-308
MICONAZOLE NITRATE 1200MG SOFT GEL VAGINAL INSERT AND 2%
EXTERNAL CREAM
ITEM 13: PATENT INFORMATION

As per 21 CFR § 314.53, we hereby submit the following patent information:

- (i) Patent Number: 5,514,698
Date of Patent Expiration: March 21, 2014

- (ii) Type of Patent: Drug Product

- (iii) Patent Owner: Ortho Pharmaceutical Corporation*, Raritan, NJ

- (iv) Patent Owner does have a place of business in the United States.

The undersigned declares that Patent No. 5,514,698 covers the formulation and composition of the miconazole nitrate 2% external vulvar cream. This product is used in conjunction with miconazole nitrate 1200 mg vaginal ovule. These two products together are the subject of this application for which OTC approval is being sought.

* Ortho Pharmaceutical Corporation is an affiliate of Johnson & Johnson. Advanced Care Products (ACP) was a division of Ortho Pharmaceutical Corporation and has since been merged into Personal Products Company.

ORIGINAL NEW DRUG APPLICATION
NDA 21-308
MICONAZOLE NITRATE 1200MG SOFT GEL VAGINAL INSERT AND 2%
EXTERNAL CREAM
ITEM 13: PATENT INFORMATION

As per 21 CFR § 314.53, we hereby submit the following pending patent information:

- (i) Attorney Docket Number: 98-40265-US
Date of Patent Expiration: Pending

- (ii) Type of Patent: Drug Product

- (iii) Patent Owner: McNeil-PPC, Inc.
Skillman, NJ 08558

- (iv) Patent Owner does have a place of business in the United States.

The undersigned declares that the Pending Patent (Attorney Docket No. 98-40265-US) covers the formulation and composition of the miconazole nitrate 1200 mg soft gel vaginal insert and the 2% external vulvar cream. These two products together are the subject of this application for which OTC approval is being sought.



Personal Products
C O M P A N Y

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



XR

April 20, 2001

NDA ORIG AMENDMENT

Mark Goldberger, M.D.
Director
Division of Special Pathogens and
Immunological Drug Products (HFD-590)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-308
MONISTAT[®] 1 Combination Pack
NDA AMENDMENT – Patent Information

Dear Dr. Goldberger,

As per 21 CFR§314.53 and our original submission of NDA 21-308 on August 31, 2000, please find enclosed updated patent information. This new patent covers the composition of the miconazole nitrate 1200 mg soft gel vaginal insert and the 2% external vulvar cream in conjunction with each other. This information is being updated because at the time of our original submission we submitted patent pending information for the combination of the 1200 mg soft gel vaginal insert and the 2% external vulvar cream (Volume 1.1 page 13-000002). The information for Patent Number 5,514,698 has not changed (original switch submission Volume 1.1 page 13-000001). Please find attached the documentation for our new patent, Patent Number 6,153,635.

Should you have comments or questions regarding this submission, please contact me directly at 908-904-3708.

Respectfully submitted,

Barbara Popek
Manager, Regulatory Affairs

DUPLICATE

EXCLUSIVITY SUMMARY for NDA # 21-308 SUPPL # _____

Trade Name MONISTAT® 1 COMBINATION PACK

Generic Name miconazole nitrate

Applicant Name Personal Products Company HFD- 590

Approval Date June 28, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / ___ /

b) Is it an effectiveness supplement? YES/ ___ / NO/ X /

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ___ / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES / / NO / /

If yes, NDA # 20-968 Drug Name Monistat 1® Dual-Pak

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**APPEARS THIS WAY
ON ORIGINAL**

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-968
NDA #
NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

**APPEARS THIS WAY
ON ORIGINAL**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #
NDA #
NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / ___ / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / ___ /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain: _____

**APPEARS THIS WAY
ON ORIGINAL**

(b) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

Signature of Preparer

/S/

Date 6/28/01

Title:

/S/

Signature of Office of Division Director

Date

6/28/01

cc:

Archival NDA

HFD- /Division File

HFD- /RPM

HFD-093/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

FDA Links Searches Check Lists Tracking Link Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

[View as Word Document](#)

NDA Number: 021308 **Trade Name:** MONISTAT 1(NICONAZOLE NITRATE)1200MG/2%
Supplement Number: 000 **Generic Name:** MICONAZOLE NITRATE
Supplement Type: N **Dosage Form:** .
Regulatory Action: OP **COMIS Indication:** TREATMENT OF VULVOVAGINAL CANDIDIASIS
Action Date: 9/1/00

Indication # 1 treatment of vulvovaginal candidiasis
Label Adequacy: Adequate for ALL pediatric age groups
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Ranges for This Indication

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
12 years	Adult	Waived	

Comments: 6/27/01 Pediatric study requirements for this application are waived because the Agency believes adult clinical trial data can be extrapolated to demonstrate safety and effectiveness in postmenarchal girls. It is unlikely that premenarchal girls would need to use this medication.

This page was last edited on 6/27/01

Signature

/S/

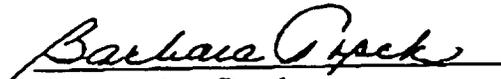
Date

June 28, 2001

NDA 21-308
MONISTAT[®] 1 Combination Pack
Miconazole Nitrate Vaginal Insert (1200 mg) and Miconazole Nitrate Cream (2%)
DEBARMENT CERTIFICATION

Certification Requirement for Approval of a Drug Product

Personal Products Company certifies that we did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Barbara Popek
Manager, Regulatory Affairs



Personal Products
C O M P A N Y

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

June 28, 2001

Mark Goldberger, M.D.
Director
Division of Special Pathogens and
Immunological Drug Products (HFD-590)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-308
MONISTAT[®] 1 Combination Pack
NDA AMENDMENT – Debarment Certification

Dear Dr. Goldberger,

As per the FD&C Act 306 and as included in our original submission of NDA 21-308 on August 31, 2000, please find enclosed a copy of our debarment certification. This debarment certification is being resubmitted as per FDA's request of June 27, 2001, to include an official signature.

We respectfully request that this information be made part of our pending New Drug Application.

Should you have comments or questions regarding this submission, please contact me directly at 908-904-3708.

Respectfully submitted,

Barbara Popek
Manager, Regulatory Affairs

**ORIGINAL NEW DRUG APPLICATION
NDA 21-308
MICONAZOLE NITRATE 1200MG SOFT GEL VAGINAL INSERT AND 2%
EXTERNAL CREAM**

CERTIFICATION REQUIREMENT FOR APPROVAL OF A DRUG PRODUCT

Personal Products Company certifies that we did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) of the Federal Food Drug and Cosmetic Act in connection with this application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Personal Products Company	DATE OF SUBMISSION 03/19/01
TELEPHONE NO. (Include Area Code) (908)904-3708	FACSIMILE (FAX) Number (Include Area Code) (908)904-3748
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 199 Grandview Road, Room SF108 Skillman, New Jersey 08558	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-308		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) miconazole nitrate, USP	PROPRIETARY NAME (trade name) IF ANY MONISTAT 1 Combination Pack	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 1-[2,4-dichloro(dichlorobenzoyloxy) phenethyl] imidazole	CODE NAME (If any)	
DOSAGE FORM: Vaginal insert & external cream	STRENGTHS: 1200 mg insert & 2% external cream	ROUTE OF ADMINISTRATION: intravaginal and external

PROPOSED INDICATION(S) FOR USE:
treatment of vulvovaginal candidiasis

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505 (B)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> PRIOR APPROVAL (PA)
REASON FOR SUBMISSION Response to FDA request.
PROPOSED MARKETING STATUS (check one) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input checked="" type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 17-450 MONISTAT 7 Vaginal Cream, NDA 20-968 MONISTAT DUAL-PAK, NDA 20-827 MONISTAT 3 Vaginal Cream, NDA 20-670 MONISTAT 3 Combination Pack, NDA 20-288 MONISTAT 7 Combination Pack, NDA 18-520 MONISTAT 7 Vaginal Suppositories

Division of Over-the-Counter Drug Products Labeling Review

NDA#:	21-308
Drug Product:	Monistat® 1 Combination Pack

Submission Date: September 1, 2000

Type of Submission: Original NDA for Rx to OTC Switch and
Labeling amendment 21-308 BL dated May 4, 2001
Labeling amendment 21-308 BL dated May 29, 2001
Labeling amendment 21-308 BL dated June 8, 2001

Sponsor: Personal Products Company (PPC)

Active Ingredient(s):

- miconazole nitrate 1200 mg (in soft gel vaginal insert)
- miconazole nitrate 2% (in external cream)

Stock Keeping Units: 1 (Combination Pack consists of 1 soft gel vaginal insert with disposable applicator and one 9 gram tube of external vulvar cream) plus Consumer Information Leaflet

Review Date: June 15, 2001

Reviewer: Arlene Solbeck
HFD-560

Project Manager: Dan Keravich

Indications:

- treats vaginal yeast infections (1-dose treatment)
- relieves external itching and irritation due to a vaginal yeast infection

Background

This is a labeling review of NDA 21-308 submitted by Personal Products Company, dated 9/01/00, for the Rx to OTC switch of miconazole nitrate (1200 mg) soft gel vaginal insert and miconazole nitrate 2% external cream. Reference is made to NDA 20-968 containing the results of the clinical trials establishing the efficacy of this combination for Rx use. The sponsor proposes to market this product OTC under the tradename MONISTAT® 1 Combination Pack as a 1-dose treatment for vaginal yeast infections which includes a topical cream for relief of associated external symptoms. The sponsor has committed to marketing the current MONISTAT®1 (tioconazole) product under a

new name and stated that the overlap in the market place of two MONISTAT®1 products would only be 3-4 weeks (memos from PPC dated 1/3/01 and 3/23/01).

The review of the submitted draft labeling follows. Reference is made to the sponsor's submission of 5/4/01 (CDER stamp date 5/7/01), consisting of proposals for revised labeling to address the agency's concern regarding correct use of the product, to the sponsor's submission of 5/25/01 (CDER stamp date 5/29/01) containing copies of the proposed Principal Display Panel (PDP) for the carton, and to the sponsor's submission of 6/8/01 containing comments to FDA's proposed changes to the Drug Facts panel, Consumer Information Leaflet and PDP. The reviewer's comments and recommendations are in accordance with the most recent prior approved labeling for MONISTAT® 3 Combination Pack (NDA 21-261), dated 5/20/00 and 9/29/00. In addition, recommendations were made for modifying the *Warnings* section in *Drug Facts* to enhance label compliance. The labeling review of the carton is in the checklist below. An example Drug Facts label is in the attachments, along with the labeling review of the external cream tube, vaginal insert blister pack, and Consumer Information Leaflet.

I. Reviewer's Comments

Information Included in the Submission

Content of Submission	Yes	No
1. A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s);	X	
2. A table of contents or index	X	
3. The most recent approved labeling *; Note: This is a new submission for an Rx to OTC switch. Reference was made to NDA 20-968 for MONISTAT® 3 Dual Pack containing a 1200 mg gelatin ovule and 2% external cream. Reference was also made to parallel labeling in NDA 18-520, NDA 20-288 and NDA 20-670		X
4. A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product.	X	
5. Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 13293. Note: Sponsor must submit information on text style and text size for Drug Facts in accordance with 21 CFR 201.66		X

*Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review: Yes No

Principal Display Panel

Paragraph 21 CFR	Description of Paragraph	Adequate (yes/no)	Comments
201.60	Principle Display Panel	Y	<ul style="list-style-type: none"> Flag in corner of top panel with the word "New" must be removed after 6 months of

Paragraph 21 CFR	Description of Paragraph	Adequate (yes/no)	Comments
			<p>OTC marketing</p> <ul style="list-style-type: none"> • The statement “with External Cream for Fast Itch Relief” must be revised. Delete the word “fast”, or use prior approved statements such as “includes cream for external relief” or “relieves associated external itching and irritation” • Delete the statement “FULL PRESCRIPTION STRENGTH” since the Rx product is no longer marketed.
201.61	<p>Statement of Identity</p> <ul style="list-style-type: none"> • Established name of drug • Statement of general pharmacological category(ies) or the principal intended actions • Bold type • Size related to the most prominent printed matter 	N	<p>Note: To be consistent with prior approved labeling</p> <ul style="list-style-type: none"> • move the phrase “Combination Pack” to follow MONISTAT® 1 on the top, bottom, front and side panels. • Revise the statement “1-Dose Treatment”: It is confusing since the external cream may be used up to 7 days. • Insert the words “and relieves associated external itching and irritation” after the words “cures most vaginal yeast infections”. • Revise the USP names for the vaginal insert and external cream as follows “Miconazole Nitrate Vaginal Insert (1200 mg) and Miconazole Nitrate External Cream (2%)”
201.62	Declaration of net quantity of contents	N	Replace word “ovule” with the word “insert”
201.1	Name and place of business of manufacturer, packer, or distributor	Y	
201.17	Location of expiration dates	Y	

Paragraph 21 CFR	Description of Paragraph	Adequate (yes/no)	Comments
201.18	Control numbers	Y	

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(c)(1)	Drug Facts, Drug Facts (continued)		
(c)(2)	Active ingredient, established name, quantity	N	<ul style="list-style-type: none"> • Revise heading to: <i>Active ingredients</i> • Delete the words "soft gel" before vaginal insert • Delete the word "in" for external cream statement
(c)(3)	Purpose	N	Use a small "a" for antifungal in "Vaginal antifungal"
(c)(4)	Use(s)	N	<ul style="list-style-type: none"> • Remove the word "repeat" from the two "Use" statements • Make sure there are at least 2 "EMS" between the end of the first bulleted statement and the second bullet in accordance with § 201.66 (d)(4)
(c)(5)	Warning(s)		
(c)(5)	(i) For external/rectal/vaginal use only	N	Place the warning "For vaginal use only" on the first line under the heading and remove period at end of statement
(c)(5)	(ii) All applicable warnings		
	(A) Allergic reaction warnings	NA	
	(B) Reye's syndrome warning	NA	
	(C) Flammability warning, with appropriate signal word	NA	
	(D) Water soluble gum warning, "Choking"	NA	
	(E) "Alcohol warning"	NA	
	(F) "Sore throat warning"	NA	
	(G) "Dosage warning"	NA	

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(c)(5)	(iii) "Do not use" followed by all contraindications	N	<p>Note: Sponsor did not provide a "Do not use" section Therefore, add the following bolded warning: Do not use if you have never had a vaginal yeast infection diagnosed by a doctor</p>
(c)(5)	<p>(iv) "Ask a doctor before use if you have"</p> <ul style="list-style-type: none"> • never had a vaginal yeast infection diagnosed by a doctor • 1 or more of the following: abdominal pain, fever, chills, nausea, vomiting, foul-smelling vaginal discharge • vaginal yeast infections often (such as once a month or 3 in 6 months) • been exposed to the human immunodeficiency virus (HIV) that causes AIDS 	N	<p>Amend the text of this section to read as follows and bold the first two bullets: Ask a doctor before use if you have</p> <ul style="list-style-type: none"> • 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
(c)(5)	(v) "Ask a doctor or pharmacist before use if you are"	N	<p>Note: This is a new subheading and warning for vaginal antifungal products containing miconazole. Add this section to read as follows: Ask a doctor or pharmacist before use if you are taking a prescription blood thinning medicine, such as warfarin,</p>

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
			because bleeding or bruising may occur
(c)(5)	<p>(vi) When using this product</p> <ul style="list-style-type: none"> • do not use tampons, douches, spermicides or other vaginal products • do not have vaginal intercourse • condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases (STDs) 	N	<p>Amend the text of this section and add a new third bullet to read as follows:</p> <p>When using this product</p> <ul style="list-style-type: none"> • 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 <p>Make sure there are at least 2 “EMS’ between the end of the first bulleted statement and the second bullet in accordance with § 201.66 (d)(4)</p>
(c)(5)	<p>(vii) Stop use and ask a doctor if</p> <ul style="list-style-type: none"> • symptoms do not get better in 3 days • symptoms last more than 7 days • you get abdominal pain, fever, chills, nausea, vomiting, foul-smelling vaginal discharge, or rash 	N	<ul style="list-style-type: none"> • Bold all three bullets <p>Amend the third bullet in the text of this section to read as follows:</p> <ul style="list-style-type: none"> • you get a rash or hives, abdominal pain, fever, chills, nausea, vomiting, or foul-smelling vaginal discharge <p>Make sure there are at least 2 “EMS’ between the end of the first bulleted statement and the second bullet in accordance with § 201.66 (d)(4)</p>
(c)(5)	(viii) Any required warnings		
(c)(5)	(ix) The pregnancy/breast feeding warning	Y	
(c)(5)	(x) Keep out of reach of children	Y	

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(c)(6)	<p>Directions</p> <ul style="list-style-type: none"> • before using this product read the enclosed consumer information leaflet for complete instructions • adults and children 12 years of age and over: <ul style="list-style-type: none"> • Soft Gel Vaginal Insert: with the applicator insert 1 Soft Gel Vaginal Insert into the vagina at bedtime • external cream: squeeze a small amount of cream onto your fingertip. Gently apply the cream onto the itchy, irritated skin outside the vagina. Use daily for up to 7 days as needed. • Children under 12 years of age: ask a doctor 		<p>Amend the text of <i>Directions</i> to read as follows:</p> <ul style="list-style-type: none"> • before using this product read the enclosed consumer information leaflet for complete directions and information • adults and children 12 years of age and over: <ul style="list-style-type: none"> • vaginal insert: with the applicator place the vaginal insert into the vagina at bedtime. 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
(c)(7)	<p>Other information and additional information not included in (c)(2) – (c)(6), (c)(8), (c)(9) of this section. Storage Statement</p>	NA	
(c)(7)	(i) Certain ingredients (e.g. Na)	NA	
(c)(7)	(ii) phenylalanine	NA	
(c)(7)	(iii) additional information	N	<ul style="list-style-type: none"> • in 1st bullet, remove the words “Soft Gel” before Vaginal Insert and revise to “vaginal insert”

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
	<ul style="list-style-type: none"> • store between 20°-25°C(68°-77°F) 		<p>Revise storage statement (4th bullet) to be consistent with tube and blister pack</p> <ul style="list-style-type: none"> • store at 20°-25°C (68°-77°F) <p>Note: The wording for the tamper-evident packaging statement regarding the tube seal is adequate. The statement “do not purchase if carton is opened” is non-specific and should be removed in accordance with 21 CFR 211.132 (c) (2). The statement regarding the vaginal insert is also nonspecific. Revise in accordance with § 211.132 (c) (2) to describe tamper-evident feature.</p>
(c)(8)	<p>Inactive ingredients</p> <ul style="list-style-type: none"> • MONISTAT® (miconazole nitrate vaginal insert) Soft Gel Vaginal Insert – gelatin, glycerin, lecthin, mineral oil, titanium dioxide, white petrolatum • MONISTAT® (miconazole nitrate cream) External Vulvar Cream – benzoic acid, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol 	N	<p>Revise as follows:</p> <p><i>Inactive ingredients</i></p> <ul style="list-style-type: none"> • vaginal insert: gelatin, glycerin, lecithin, mineral oil, titanium dioxide, white petrolatum • external cream: benzoic acid, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol
(c)(9)	Questions	N	<ul style="list-style-type: none"> • The telephone number reference (1-877-Monistat) and website reference (www.monistat.com) need to be modified. The product name should not be in the Drug Facts box.

Labeling Content [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
			<ul style="list-style-type: none"> Only the phone number should be bolded in this statement.

Labeling Format [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(d)(1)	Drug Facts: first letter of words uppercase	Y	
(d)(1)	Headings, subheadings: first letter of first word uppercase	Y	
(d)(1)	Left justification	Y	
(d)(2)	Drug Facts type size greater than largest type size used in Drug Facts labeling	N	Sponsor must submit type size
(d)(2)	Heading 8 pt or 2 point sizes greater than text point size	N	Sponsor must submit type size
(d)(2)	Type size 6 pt size for information in Drug Facts	N	Sponsor must submit type size
(d)(2)	Subheadings ≥ 6 point type size	N	Sponsor must submit type size
(d)(2)	Drug Facts (continued) type size no smaller than 8-point type	N	Sponsor must submit type size
(d)(3)	No reverse type	Y	
(d)(3)	Letters do not touch	Y	
(d)(3)	≥.5 pt leading (space between lines)	Y	
(d)(3)	No more than 39 characters per inch	Y	
(d)(3)	Bold Italic headings and title	Y	
(d)(3)	Bold subheading except (continued)		
(d)(3)	Black or dark type	Y	
(d)(3)	White or neutral background	Y	
(d)(3)	Contrasting dark color for title and heading	Y	
(d)(4)	Bullet: solid circle or square 5 pt type, same shape and color, left justified or separated from heading or subheading by at least two square "EMS"	N	Sponsor must submit bullet size
(d)(4)	Bullet on same lines: end of statement separated from bulleted statement by two "EMS"	N	<i>In Uses, When using this product and Stop use and ask a doctor if sections, second bullets seem too close to end of statement of first bullets</i>
(d)(4)	Bullet on same lines: additional bulleted statement does not continue on next line	Y	
(d)(4)	Vertical alignment of bulleted statements	Y	

Labeling Format [21 CFR 201.66 (c)]

Paragraph	Description of Paragraph	Adequate (yes/no)	Comments
(d)(5)	Appear on more than one panel	Y	
(d)(5)	Visual graphic signals continuation	Y	
(d)(6)	Left justification of information required by (c)(2)	Y	
(d)(6)	Right justification of information required by (c)(3)	Y	
(d)(6)	Alphabetical order of active ingredients	Y	
(d)(6)	Information required by (c)(4), (c)(6) - (c)(9) may start on same line as required headings	Y	
(d)(6)	None of information required in (c)(5) shall appear on same line as Warnings	Y	
(d)(7)	Graphical images should not interrupt the heading, subheading and information. Hyphens should not be used except to punctuate compound words.	Y	
(d)(8)	Enclosed box using barline	Y	
(d)(8)	Horizontal barline separates headings listed in (c)(2) - (c)(9)	Y	
(d)(8)	Horizontal hairline precedes heading immediately after Drug Facts	Y	
(d)(8)	Horizontal hairline follows the title	Y	
(d)(8)	Horizontal hairline extending within 2 spaces on either side of the Drug Facts box shall immediately follow the title and precede the subheadings set forth in (c)(5) [except (c)(5) (ii) A - G]	Y	
(d)(9)	Directions in table format when dosage instructions are provided for three or more age groups or populations	NA	
(d)(9)	Horizontal barline preceding the next heading may end the table	NA	

II. Agency Recommendations

- A. The reviewer's comments and recommendations for revisions found in the above checklist for the carton labeling and on the attachments for the external cream tube labeling, vaginal insert blister pack labeling and Consumer Information Leaflet may be conveyed to the sponsor.

- B. The Agency notes that if any additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.
- C. The Agency is developing class labeling for all OTC vaginal antifungal products. When the guidance is finalized, we recommend that the sponsor draft the labeling for this product according to the format used in the Agency's final guidance document.

/S/

6/21/01

Arlene Solbeck, MS
IDS/Biologist, HFD-560

/S/

> 6/21/01

Helen Cothran, BS
Team Leader, HFD-560

Attachments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: June 28, 2001

From: Brad Leissa, M.D.
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: NDA 21-308 (Monistat 1 Combination Pack)

NDA 20-968, Monistat Dual-Pak (miconazole nitrate 1200 mg soft gel vaginal insert and miconazole nitrate 2% cream – for external vulvar use) was approved for prescription use on June 30, 1999.

When the applicant McNeil-PPC approached the Agency about the conditions for an Rx to OTC switch, they were told that an actual use study would help determine whether women could appropriately self-select and self-manage their vaginal condition with this product in an OTC setting. McNeil-PPC agreed to conduct the study and the data from this actual use study were submitted to NDA 20-968. As addressed in the Medical Officer Review by Linda Hu, M.D., this actual study raised concerns about consumers' ability to comprehend labeling. The women studied did not appropriately self-select and manage their illness based on the labeling instructions provided. (The labeling tested in this study pre-dated the finalization of the Drug Facts Format OTC labeling requirements.)

In light of these concerns, McNeil-PPC has committed to conduct a Phase 4 study that will assess consumers' Monistat 1 Combination Pack labeling comprehension using revised labeling consistent with the Drug Facts Format (carton) and the draft labeling guidance for VVC OTC drugs (consumer information leaflet).

At the time this NDA was submitted, we were aware that another Monistat 1 product (tioconazole ointment – a different active ingredient) was being marketed by McNeil-PPC on the behalf of Bristol-Myers Squibb (BMS). We raised concerns with McNeil-PPC that this could cause confusion for consumers. BMS (the NDA holder for tioconazole ointment) recently submitted a labeling supplement requesting a trade name change from "Monistat 1" to "Day 1". This action will help to minimize consumer confusion.

I concur with the reviewing medical officer, Dr. Linda Hu, that this NDA can be approved with the knowledge that the Phase 4 commitment study should help to clarify why consumer self-selection problems exist. Do women not understand the labeling or do they understand it but choose to ignore the labeling recommendations?

I suspect that these self-selection concerns are not limited to Monistat 1 Combination Pack but reflect labeling comprehension issues for vulvovaginal candidiasis products as a class in the OTC environment.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

DEC 4 2000

MEMORANDUM OF TELECON

DATE: November 2, 2000

APPLICATION NUMBER: NDA 21-308

PRODUCT PROPOSED NAME: Monistat 1 Combination Pack (miconazole nitrate) 1200 mg vaginal ovule and 2% external vulvar cream

BETWEEN: Sponsor: Personal Products Company
Phone: 908-904-3745
Barbara Popek, Manager, Regulatory Affairs
Cathleen Lamia, Manager, Biostatistics
Tian Zhao, Scientific Programmer

AND FDA: Division of Special Pathogen and Immunologic Drug Products, HFD-590:
Christina H. Chi, Ph.D., Regulatory Project Manager

Division of Over the Counter Drug Products, HFD-560:
Linda Hu, M.D., Medical Officer

SUBJECT: FDA's request for electronic Reviewer's Aid and additional safety data.

To aid the review of pending NDA 21-308, the Agency requested the following items:

1. Text and tables of at least the first three volumes of August 31, 2000 submission as a Word 97 file on CD-ROM.
2. Actual use trials data in an Excel 97 file and a SAS transport file version 6.12, with 3 hard copies of a code book defining tables and variables as well as listing values of each variable.
3. Updated marketing information in the same format as the table provided in Appendix 2 of the Report (Vol 1.2 pp. 08-263): listing countries where the miconazole nitrate 1200 mg vaginal ovule is marketed; local tradename; marketing status (prescription or OTC and note whether the product is pharmacist dispensed); first approval date; marketing launch date; the total number of units sold or distributed; withdrawal date if applicable and the reason for withdrawal.
4. Safety profile update:
 - Literature search on the miconazole nitrate 1200 mg vaginal ovule for safety (any adverse drug reaction associated with the use of the product) with summaries of articles.

- FDA adverse event data for the miconazole nitrate 1200 mg vaginal ovule product with serious Adverse Event (AE) and deaths in a separate table, as well as case reports or MedDRA forms for serious case or deaths.
- Both Canadian and the United Kingdom's equivalent of the Agency's AE reporting for the miconazole nitrate 1200 mg vaginal ovule product as well as case reports for serious cases or deaths.
- The United States' Consumer Adverse Events reported to the toll free number for adverse drug reaction reporting for the miconazole nitrate 1200 mg vaginal ovule product.
- Updated World Health Organization's (WHO) databases through the time of the NDA submission.

5. Please clarify the following:

- That all the miconazole nitrate 1200 mg vaginal ovule products are identical in formulation
- The time period covered by the WHO report.

The sponsor responded that item # 1 would be sent to the Agency by November 15, 2000, and the rest could be made available by November 30, 2000.

The telecon was adjourned amicably.

/S/

Christina H. Chi, Ph.D., *1*
Project Manager, DSPIDP (HFD-590)

- 12/4/2000

/S/

Concurrence: Linda Hu, M.D., *12/4/00*
Medical Officer, DOTCDP (HFD-560)

cc: Orig. (archival) NDA 21-308

HFD-560/Div. Files
HFD-560/ MO/LHu(12/4/2000
HFD-560/PM/DKeravich

HFD-590/Div. Files
HFD-590/PM/CChi

Drafted by: CChi/November 2, 2000

Final: 12/4/2000