

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

- *APPLICATION NUMBERS:* **20-827**

ADMINISTRATIVE DOCUMENTS

ORIGINAL NEW DRUG APPLICATION
NDA 20-827
MICONAZOLE NITRATE (4.0%) VAGINAL 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:** Advanced Care Products, Ortho Pharmaceutical Corporation, Raritan, New Jersey

- (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 MONISTAT[®] 3 (miconazole nitrate 4.0%) Vaginal Cream. This product is the subject of this application for which approval is being sought.

APPEARING THIS WAY
ON ORIGINAL

ORIGINAL NEW DRUG APPLICATION
NDA 20-827
MICONAZOLE NITRATE (4.0%) VAGINAL CREAM
CLAIMED EXCLUSIVITY

Advanced Care Products is claiming marketing exclusivity for MONSITAT® 3 (miconazole nitrate 4.0%) Vaginal Cream. Reference is made to 21 CFR § 314.108(b)(4).

(i) *New Clinical Investigations*

To the best of our knowledge, each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR § 314.108(a).

(ii) *Essential to Approval*

In our opinion there are no published studies or publicly available reports exist which would provide a sufficient basis for the approval for which Advanced Care Products is seeking approval without reference to the new clinical investigations in this application.

The FDA's Division of Anti-Infective Drug Products requires that each new formulation seeking OTC approval be shown to be therapeutic equivalent to an existing OTC 7-day therapy.

(iii) *Conducted or Sponsored By*

Advanced Care Products was the sponsor named in the Form FDA 1571 for [REDACTED] under which the new clinical investigations that are essential to the approval of this application was conducted.

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EXCLUSIVITY SUMMARY for NDA # 20-827 SUPPL # X

Trade Name Mopistat [®] 3 Generic Name miconazole nitrate ~~powder~~ cream #2
Applicant Name Advanced Care Products HFD-590
Personal Products Company
Approval Date March 1998

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 1 / / NO 1 / /

b) Is it an effectiveness supplement?
YES 1 / / NO 1 / /

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

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 1 / / NO 1 / /

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 / /

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

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8 (even if a study was required for the upgrade).

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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 / / NO / /

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

NDA # 17-450 18-520

NDA # 18-888 20-288

NDA # 20-670 18-592

2. Combination product. N/A

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

YES / / NO / /

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

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 8.

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

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 / /

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ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES / / NO / /

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

YES / / NO / /

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 95-005

Investigation #2, Study # 95-007

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

APPEARS THIS WAY
ON ORIGINAL

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 95-005

Investigation #_, Study # 95-007

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 95-005!

IND YES / NO / / Explain: _____

Investigation #2 95-007!

IND YES / NO / / Explain: _____

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A !

YES / / Explain _____ ! NO / / Explain _____

Investigation #2 *N/A* !

YES / / Explain _____ ! NO / / Explain _____

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

YES / / NO / ✓

If yes, explain: _____

/S/

PhD March 25, 1998

Signature

Date

Title: *Senior Researcher*

/S/

3/31/98

Signature of ~~Division~~ Director

Date

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-827

Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

Monistar 3 miconazole nitrate

rFD-520 Trade and generic names/dosage form: Vaginal Cream 4% Action AP AE NA

Applicant Advanced Care Products Therapeutic Class Anti-fungal

Company Personal Products
Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate N/A inadequate

Indication in this application Vulva Vaginal (For supplements, answer the following questions in relation to the proposed indication.)
Conditionisic

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. Labeling indicates "do not use in girls under age 12"
5. If none of the above apply, attach an explanation, as necessary. **Safety and effectiveness in pediatric patients have not been established.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

IS/
Signature of Preparer and Title Ph.D. Project Manager

March 25, 1998
Date

cc: Orig NDA/PLA/PMA # 20-827
HFD-520/Div File
NDA/PLA Action Package
HFD-006/ SOLmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 6/5/97)

**ORIGINAL NEW DRUG APPLICATION
NDA 20-827
MICONAZOLE NITRATE (4.0%) VAGINAL CREAM
DEBARMENT CERTIFICATION**

CERTIFICATION REQUIREMENT FOR APPROVAL OF A DRUG PRODUCT

Advanced Care Products 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.

APPROVED
ON 07/01/87

APPROVED
ON 07/01/87

MAR 26 1998

NDA LABELING REVIEW**Division of Over-the-Counter Drug Products****NDA#: 20-827****DRUG PRODUCT: Monistat® 3 Vaginal Cream****ACTIVE INGREDIENT: Miconazole nitrate cream (4%), 200 mg per prefilled applicator****INDICATION: "For the treatment of vaginal yeast infections (candidiasis)"****SPONSOR: Advanced Care Products****TYPE OF SUBMISSION: Original New Drug Application****DATE OF SUBMISSION: March 31, 1997****DATE OF REVIEW: March 12, 1998****REVIEWER: Cheryl Turner, IDS****PROJECT MANAGER: Sakineh Walther**

Advanced Care Products (ACP) submitted an NDA on March 31, 1997, to provide for the Over-the-Counter marketing of MONISTAT® 3 Vaginal Cream, miconazole nitrate cream, (4%), a 3-day drug treatment for vaginal antifungal infections. Draft labeling was also submitted. On January 29, 1998, an amendment to the pending original NDA was submitted, which contains the mock-ups of draft labeling and educational brochures for this NDA. The sponsor states that the labeling developed for this NDA parallels that of the OTC labeling for MONISTAT® 7 Vaginal Cream (NDA 17-450), MONISTAT® 7 Vaginal Suppositories (NDA 18-520), MONISTAT® 7 Combination Pack (NDA 20-288) and MONISTAT® 3 Combination Pack (NDA 20-670), with the exception of the instructions pertinent to the use of each type of applicator.

For this application, the sponsor is only considering the OTC marketing of the prefilled applicators. Changes to sponsor's initial proposed labeling have been incorporated into the final labeling. See Attachment 1. These changes were made after Agency review and communications between the Agency and the sponsor.

In the FEDERAL REGISTER of February 27, 1997, the Agency published a notice of proposed rulemaking to establish a standardized format for the labeling of OTC drug products. This proposal is intended to enable consumers to better read and understand OTC drug product labeling and to apply this information to the safe and effective use of OTC drug products.

We recommend that the sponsor draft the label in the new proposed OTC labeling format. In the Agency's final rule for this new labeling format, which is expected to be published soon, headings and subheadings will be in bold type and upper and lower case letters. The heading and subheading information is presented in a bulleted format. The headings should be bolded and presented in the following order: **Active Ingredient(s), Purpose(s), Use(s), Warning(s), and Direction(s)**. Note that no other information should precede "Active Ingredients". The term "Use" is used instead of "Indication." "Warnings" should precede "Directions." In addition, the Helvetica type style should be used and the type size should not be less than 6 points.

For this specific MONISTAT 3 label, text and headings should not have all capital letters anywhere in the labeling. Bolding should be used in headings only, unless we have indicated that a specific portion of the labeling should be emphasized with bolding. As a heading, we recommend that "INDICATION" be changed to "Use".

The Agency is also developing class labeling for all OTC vaginal antifungal products. When the class labeling for OTC vaginal antifungal products is finalized, it is expected that all such products will conform to the class labeling guidance when issued. Further, all OTC labeling is expected to conform to the labeling requirements for OTC drug products when the final rule is published.

Recommendations:

Carton

1. Final labeling for MONISTAT 3 should be consistent with the mock-up version in Attachment 1.
2. ACP requested that the line of text in the Top and Bottom panels be changed to: "If you have questions or comments, please call 1-888-MONISTAT. ACP also requested that an appropriate icon such as a telephone or question mark be inserted in front of that statement.

Educational Brochure

1. Under the Directions for Use, the Agency agreed that ACP could include in the text a reference to inserting the prefilled applicator while standing up. The illustration will only be of the woman in the recumbent position, with text referencing the illustration as well.
2. The order of the information in the educational brochure information should be presented as submitted in the sponsor's mock-up (1/29/98).

Overwrap

1. Active ingredient: miconazole nitrate 200 mg per applicator should be inserted right after the statement of identity.
2. Lot number and expiration date must be included on each overwrap.
3. ACP informed the Agency that they have remaining batches of the overwrap as submitted and requested permission to continue to use them until the next printing. The Agency agreed to the request if a sticker will be placed on each overwrap listing the SOI as described in this review, and the active ingredient as 200 mg miconazole nitrate per applicator. ACP also stated that the next printing of the overwrap will occur in two months.

Warnings section in both the Carton and Educational Brochure

Note that the keep out of reach of children and the accidental ingestion warnings should use the language currently specified in section 330.1(g) of the Code of Federal Regulations (CFR), until such time as the OTC Labeling Requirements is final.

Statement of Identity (SOI)

1. The sponsor requested that the SOI for this product remain as miconazole nitrate vaginal cream. "Miconazole Nitrate Cream" is an official drug that is recognized in the United States Pharmacopeia (USP). As such, labeling must use the USP name exactly for the SOI. Section 502(g) of the Federal Food, Drug, and Cosmetic Act states that an official drug is deemed to be misbranded if it is not packaged and labeled as prescribed therein. One way to fulfill the requirements and retain reference to vaginal cream is shown below:

Miconazole Nitrate Cream
Vaginal Cream

2. The SOI must be prominently displayed. Therefore, we recommend that the SOI be 1/2 the size as the brand name in all areas of the labeling, *although this is not a regulatory requirement.*

/S/

Cheryl Turner, R.N., IDS

/S/

Helen Cothran, B.S., Team Leader

/S/

Ling Chih, M.D., M.P.H.

/S/

Linda M. Katz, M.D., M.P.H. *3/26/98*

/S/

3/26/98

DDMAC REVIEW

NDA #: 20-827
Drug: Monistat 3 Vaginal Cream (NDA-827)
Sponsor: Advanced Care Products
Study: Label Comprehension Study Among
Dated: July 17, 1997
Reviewer: Karen Lechter, J.D., Ph.D.
Reviewing Div.: HFD-40
Review Completed: September 8, 1997

Objectives

The materials state that "the objective of the study is to gather information regarding the communication of the existing labeling format for over-the-counter vaginal yeast infection products." It does not contain specific communication objectives to serve as the basis for evaluating whether the questionnaire appropriately addresses those objectives.

Methodology

The study will be conducted in 20 geographically dispersed malls throughout the continental US.

Participants

Participants will be 400 women age 18-49. As about 50% of women have suffered from a yeast infection at some time, it is estimated that approximately half the sample (200) will have had yeast infections.

Analysis

Data will be analyzed for the group as a whole and for the subgroups of those who have had and those who have not had yeast infections.

Procedure

Participants will read the package labeling (i.e., carton label) and will then be asked questions about it while it is present. The package labeling will be removed and participants will then read the insert and answer similar questions about that.

Comments

It is not clear what the purpose of this study is, and which issues are important to test. The best way to evaluate the proposed label is to use a control label for comparison, to

see how the proposed label fares in comparison to another that might be used instead.

Further, without specific communication objectives, it is impossible to determine whether the questionnaire is addressing the important issues and is doing so in an appropriate manner. Communication objectives should be fairly specific to guide design of the label and development of an appropriate questionnaire.

As many women may be reluctant to provide their exact ages, I suggest asking for their ages in terms of ranges that do not pinpoint the exact age.

Many of the questions in the questionnaire would be best asked by using scenarios. By presenting a situation to a participant and asking her what the person in the scenario should do, the questionnaire can avoid leading questions and can tap whether participants truly understand the information on the label.

It would be advisable to avoid asking questions that require participants to list a number of items in their responses. For example, Question 1 asks who should consult with a doctor before using the product. Our experience has been that open-ended questions such as these result in only a few correct answers being given, and the scoring systems do not usually take into account how many correct responses are given by each person. Therefore, the results are not very helpful. We recommend that more use of scenarios be made for such questions, asking, in a non-leading manner, whether persons in particular situations should see a doctor. Less desirable but superior to the open-ended question for this type of issue would be a checklist type of question that included persons who should and those who need not consult a doctor. Other questions in the protocol that now require respondents to list a number of responses are best handled with scenarios; otherwise checklists (with both correct and incorrect items) are more appropriate than open-ended questions.

Question 7 asks whether the product should be applied to the eyes or taken by mouth. A question that combines two items like this and that requires only a yes or no response does not adequately test whether or not participants understand the question. It would be better to separate these two items and to intersperse them with items that are correct if answered "yes."

Questions 8-13 for the package label, and the corresponding questions for the insert are best handled by scenarios; alternatively, some could be in the form of checklists. Questions 9a and 10a are leading and may not result in meaningful responses. Most people who have not read the label would be able to respond correctly. For that reason, scenarios may be a better approach to asking about these issues.

A question such as Question 11a is well-suited for a scenario format. Several scenarios could be given, with women who have used the product not getting better within several different numbers of days. The question should ask what these women should do. Other questions fit equally into the scenario format.

It is important when checklists are given that approximately equal numbers of items should be answered "yes" and "no." Otherwise, there is a danger of creating a response set that would make it more likely that the most common response would be given.

Scenarios often should be accompanied by open-ended questions; in some cases multiple-choice questions would also be appropriate.

I am unable to comment on the adequacy of the questionnaire in terms of topics it covers. Dr. Chin and Dr. Davis may address the issue of whether important elements of the label have not been addressed adequately.

There are some questions on the portion covering the carton label that are not asked about the insert, and vice versa. I wonder whether or not this was intentional, and if it was, why were some topics chosen to be asked only once and others were asked twice.

The questions asking about the participant's employment and number of members in the household are not relevant to label comprehension. They can be eliminated unless the sponsor has some other use for them.

It appears that no particular efforts have been made to recruit persons of low education or low comprehension who may use this product. It is essential that there be sufficient numbers of such persons to be analyzable statistically as a group. The regulations for non-prescription products require that persons of low comprehension be able to understand the label. This study will not provide information on that issue unless specific measures are undertaken to recruit such persons.

It would be advisable to limit recruitment to women who are potential candidates for use of the product; i.e., those who have had previous diagnoses of vaginal yeast infections. It is this population that should be tested for comprehension.

It is important to simplify the language of the questions to enable persons with low comprehension to understand them. If the label is being redesigned, language simplification should be a goal there, as well. Therefore, words such as "consult," "medication," "adverse reactions," and others should be eliminated in favor of simpler wording in both the labeling and the questionnaire.

Comments on Labeling

Carton Label

- It would be best to put the proposed label in the Drug Facts format, as eventually, this class of drugs will be in that format.
- The statement on the back about "the convenient 3 day cure" is promotional and should not appear on the back of the carton.

- The statements in all upper case letters should be changed to upper and lower case and bolded instead or highlighted by color, in accordance with the proposed label format regulation and consistent with industry recommendations.
- "Indications" should be changed to "uses." Other language in this statement should be simplified.
- Advice to read the insert and where to call for questions should be placed in accordance with the Drug Facts format proposal.
- Instructions to spread the cream on the "vulva" may not be understood by many users. Further explanation, in simplified language, should be provided.
- Warnings should be in the proposed Drug Facts Format, with upper and lower case lettering.
- Language should be simplified throughout, such as "consult," "medication" "ingestion" "punctured" "embossed."
- Reasons for not using tampons should be given. Consumers are more likely to heed such warnings if they understand why they are begin given.
- It may be helpful to make it clearer to users that the product will not cure them in three days and that it may take several more days for complete relief. Unlike most products on the market, this one continues to work for some time after the last dose is taken. Perhaps that can be clarified on the label.

Insert

- Some comments made for the carton label are also applicable to the insert. They will not be repeated in this section.
- Language could be simplified in several places. For example "release pressure" could be replaced by "stop squeezing." The words "adverse reactions" can be eliminated. They serve no purpose if "side effects" is used. If abdominal cramping is the same as stomach pain or cramping, it would be better to use the simpler terms in describing this potential side effect. "Penile itching" should be changed to "itching of the penis" since "penile" is not a word with which all readers would be familiar.
- It may be helpful to users for the diagrams for standing up and lying down to be labeled as such.
- Distinctions should be made between actions that should not be taken while undergoing treatment for the vaginal infection, and steps that should be taken to prevent future infections. The "For Best Results" section mixes the two types of advice. For example, some items should be followed after the infection is gone, such as the use of cotton underwear, changing out of wet clothes, and advice about douching. It would be most helpful to consumers to understand which of these measures can help prevent future infections.
- As some users will not understand "vulvar," a definition or simplified explanation should be provided as well as a diagram to clarify which area this is.

/S/

Karen Lechter, J.D., Ph.D., HFD-40, Division of Drug Marketing, Advertising and Communications

DDMAC REVIEW

NDA #: 20-827
Drug: Monistat 3 Vaginal Cream
Sponsor: Advanced Care Products
Study: Revised Draft Protocol for Label Comprehension
Dated: November 17, 1997
Reviewers: Karen Lechter, J.D., Ph.D.
Reviewing Divs.: HFD-40
Review Completed: February 23, 1998

The document that is reviewed contains the sponsor's response to the agency's comments on the initial protocol, the questionnaire for the label comprehension test, the analysis plan, and revised labeling.

Sponsor's Response to Agency Comments

The sponsor's responses to agency comments were generally acceptable. However, responses were not given regarding all of the suggestions made in the reviews by the agency. These suggestions remain unaddressed by the sponsor and are relevant to the study.

Although the sponsor indicates that the population will be a representative sample, it will be important also to have a cohort of persons who function at a low level of literacy. The regulations for OTC drugs require that labels be comprehensible to persons of low reading comprehension [21 CFR 330.10(a)(4)(v)]. Therefore, there should be sufficient numbers of these types of persons in the study to conduct a separate analysis on them.

One agency comment in an earlier review was that the communication objectives were not specified. The response provided general communication objectives, but they were not as specific as they could be. For example, one communication objective is "what is the intended use of this product." A more useful and specific objective would be "This product is only for women who have had similar symptoms previously diagnosed as vaginal yeast infections." The failure to list such specific objectives is not serious; however, more specific objectives help guide the creation of the questionnaire and the analysis of the results. The questionnaire as currently proposed does not completely test knowledge of who should use the product.

The sponsor was responsive to some of the labeling suggestions. However, some of the suggested new wording includes phrases that may be difficult for readers to understand. Efforts should be made to simplify the wording in the final labeling along the lines that have been discussed recently within the agency. We may want to send specific suggestions to the sponsor for wording of the labeling.

Methodology

As the Drug Facts format will be used for the final product label, a comparator label in another format is not necessary for this study. However, we welcome the sponsor's thoughts about the usefulness of a comparator.

Persons who are considered to be of low literacy should be included in sufficient numbers to be analyzed as a separate group. At least 20-25% is suggested.

There should be approximately 50% of participants who have had a prior episode of vaginal yeast infection.

As the label will indicate that the product can be used by girls age 12 and above; 12-18 year olds should be included in the study.

Questionnaire

These comments on the questionnaire reflect the thoughts of HFD-560, HFD-590, as well as those of HFD-40.

In response to agency comments, the sponsor has included a number of questions in a scenario format, and it has added some new questions as well.

The questionnaire does not ask participants if this product would be appropriate for them to use themselves if they experience symptoms of a vaginal yeast infection. This information would be useful in conjunction with the medical information that is collected on each participant. One rationale for the sponsor to include persons who have not experienced at least one prior vaginal yeast infection is to determine whether they can appropriately conclude that they should not use the product without first consulting a physician. However, there are no questions asked as to whether the individual respondent is a candidate for use of this product and why they made the choice they did. Such questions should be included. They should be phrased in a non-leading manner.

The questionnaire itself appears to be quite long. The sponsor should determine how long it would take to complete it and consider shortening it if it is more than 20-30 minutes. It is not necessary to repeat questions about the insert if they were already asked about the carton label.

Some of the language of the questionnaire can be simplified, which may be helpful to persons with less education. We suggest changing "consult" to "talk", "medication" to "medicine," "apply" to "use," "experience" to "have" or "had." We suggest in Q. 26b that "adverse reactions or side effects are experienced" should be simplified to "you have

side effects."

As this study is to assess how well potential users will understand the label, and not how they would use it, it is advisable to change the language of the questions to ask "How should you..." rather than "How would you...." Such language appears in the following questions: 8, 9a, 9b, 9c, 10b, 10c, 11b, 11c, 12, 13a, 13b, 13c.

Although Attachment 1 of the document indicates that ages will be requested in terms of ranges (p.2), the questionnaire has not been changed to reflect that fact.

Care should be taken in the way in which potential participants are recruited and given information about the study so as not to bias them.

We suggest referring to the "carton," rather than to the "package label" in presenting the materials to participants. This language is more user friendly for consumers. Such language can be used in 4a, 4b, and many subsequent questions.

The following are comments on specific questions:

Q.4a. We suggest asking participants to read the carton label as if they were in a store contemplating purchase, since a store situation is where most of the important selection information is processed. The agency prefers participants to have this orientation.

Q.6. We suggest adding the following to the list of persons who might talk with a doctor before use:

- women who have never had a yeast infection. [This is a major group of potential users who should see a doctor before use.]
- women who have a fever (higher than 100 degrees F orally). [A definite temperature should be specified in the question, as it appears on the label with a specific temperature. Any temperature of 100 degrees or higher can be used in this question—it need not be exactly 100.]
- women who have abdominal or lower back pain
- women who have a vaginal discharge that smells bad

The last 3 of these items bulleted above should then be removed from Q.7. Further, additional items that would not require consultation with a physician should be added to the list in Q.6, so it is not so heavily weighted toward "yes" answers.

Q.7. We suggest rewording Q. 7 to say: "According to the label, for each of the following cases, is this product OK to use or not OK to use?"

After removing those items from Q. 7 that have been added to Q.6, we suggest adding to Q.7 those items from Q.17 that do not already appear in Q.7. These include the

items involving:

- women who are pregnant
- women who are on a diet
- women who have frequent yeast infections
- women who smoke
- women who are using birth control pills [This item originally said "estrogens."]
- women who have yeast infections that don't clear up easily

As we mentioned earlier, we recommend eliminating Q.17, as this topic would have been covered with regard to the carton label.

Q.9b. This question should ask: "According to the label, how many times a day should you use this product?" An additional question should be asked: "According to the label, for how many days should this product be used?" It would be best then to ask Q.9a concerning the time of day for use.

Q.9c. We suggest wording this: "According to the label, should you use this product 3 days in a row, or is it OK to skip days in between uses?"

Q.10a. This should be a separate question (Q.10.), with the original questions 10b. and 10c. changed to 11a. and 11b. This question (10.) discusses expectation of benefit, while the others discuss possible actions if there is no improvement.

From this point on, questions should be renumbered

Q10b.(new 11a.) We suggest wording this: "What should you do if you did not have the improvement you expected?"

Q.10c. (new 11b.) We suggest something like the following wording: "When would you do this?"

Q.11a. (new 12.) We suggest rewording this question to say: "If you were using this product, how soon after you start using it would you expect to get well—that is, have no more symptoms?"

Q.11b. (new 13a.) We suggest wording such as the following: "What should you do if you didn't get well...?"

New Q.13b. We suggest asking something such as the following: "When would you do this?"

Q.12. (new 14.) This question asks what the woman would do if her symptoms returned. It does not specify a time frame. We suggest asking: "What should you do if

your symptoms returned within 6 weeks?"

Q. 13a-c. (new 15a.-c.). Each of these questions should mention a single adverse event and ask what the woman who has it should do. They should not be combined as they are in Q13a. All of these items require a response of consulting a physician. In order to avoid a response bias, it would be best to include one or more items that do not require the same response. To keep the questionnaire shorter, it is not necessary to ask about every side effect in the "Ask a Doctor" section of the labeling.

Q.13c. (new 15c.) A specific temperature of 100 degrees or higher should be indicated, such as 100 or 101 degrees F, as the label indicates a specific temperature.

Q.14a. (new 16a.) This question refers to the insert. At this point, the insert has not been shown to participants. The question should refer to the carton label instead. We suggest rewording the question to say: "Does the carton label say anything about using tampons while treating yourself with this medicine?"

Q. 14b. (new 16b) We suggest "using tampons" instead of "wearing tampons." Questions 14a. and 14b. might be asked in a better way, without leading questions, by using scenarios of a person who wants to use tampons for her period or some other reason while using the medication, and asking what she should do.

When the insert is presented, we suggest saying something like the following:

"Here's an educational brochure that is in the carton. Please take a few minutes to read the information as you would if you were at home. Take your time and let me know when you're finished." Rather than saying "insert," which is somewhat of a technical term, we suggest referring to the insert throughout the questioning as an "educational brochure."

As noted earlier, we suggest eliminating all questions asked about the insert that have already been asked about the package label. The questionnaire as now written is quite lengthy and may result in participant burnout as it progresses. We suggest asking only questions about new information once the insert is presented.

Q. 26a. We suggest eliminating this question.

Q. 26b. We suggest eliminating this item as it is now written. In different places on the insert it states to stop use and consult a doctor for some adverse reactions, but for others (e.g., temporary increase in itching), it does not state clearly what should be done. This question can be replaced with a question that we propose asking after 26c. (See comments below.)

Q. 26c. (renumber) We suggest changing this to read "According to the educational brochure, which of the following side effects may occur with the use of this medicine? For each one, answer 'yes' if it may occur according to the brochure or 'no' if it is not mentioned."

We suggest then asking: "If you have any of the side effects mentioned in the brochure, what should you do? For each possible side effect I am going to read you, answer whether you should continue using the product, stop using the product, stop using and ask your doctor, go immediately to the emergency room, or stop use and restart after a few days." [Show card with these statements.] For this question, a sampling of adverse events should be provided from the category requiring stopping use and consulting a doctor as well as from the category permitting continued use.

Q. 27a. (renumber) This question should ask the following: "Have you ever had a vaginal yeast infection?" It should be coordinated with questions 30a.-c. (original numbering).

Q.27b. (renumber) We suggest the following wording: "When did you have your last vaginal yeast infection? Specify....."

Q.-27c. (renumber) We suggest rewording this to say: "How many times have you had a vaginal yeast infection within the past 6 months?"

**Q.29b. (renumber) We suggest adding 29c., as follows:
"The last time you used the product(s) you mentioned, for how many days did you use it (them)?" The questionnaire should provide a column to indicate what this response was for each product used.**

**We would also be interested in responses to the following question:
"Why did you choose the last product you used instead of other products that were available?" We hope by this question to learn whether consumers are responding to the length of treatment or to other features of the products in making their selections. The sponsor may be able to suggest better wording for this question.**

Q. 30a. (renumber) We suggest changing the wording to: "Has a doctor or other health care professional ever diagnosed that you had a vaginal yeast infection?"

Q. 30b. (renumber) An additional question is suggested as follows:

"Have you talked to or visited any of the following about your vaginal symptoms?"

	<u>YES</u>	<u>NO</u>
Doctor		
Nurse		
Pharmacist		
Midwife		
Physician Assistant		
Nurse Practitioner		
Clinic		
Health Food Store		

Questions A1, A2, and B. are not necessary for purposes of label comprehension, and can be eliminated if the sponsor has no reason to ask them for other purposes.

Analysis Plan

The analysis plan associates each communication objective with its related questions. This is helpful in planning the analysis. However, the plan also states that 80% scoring correctly for most questions, and 50% scoring correctly on one set of questions would satisfy the objectives. The agency is reluctant to institute *a priori* objectives at this time, and would rather look at the importance of each question, and which communication objective is being tested. For key communication objectives, it would be important that most of the participants are able to answer the questions correctly. For information that is less critical, it may be acceptable that fewer participants answer those questions correctly. The results of these questions should be used as a guide for improving the labeling, and strict criterion scores are not necessary.

The analysis should look separately at the following subgroups:

- low comprehension
- previous diagnosis/no previous diagnosis

Consideration should also be given to analyzing some questions based on the medical information collected in questions 27 and 30. For example, are correct responses to key questions correlated with the number of times the woman has had a vaginal yeast infection or with the recency of the last infection? Is a correct response to whether or not the respondent can use the product correlated with any of the personal medical information?

Conclusion-Label Comprehension Study

The sponsor has responded to many of the comments made in the agency's earlier reviews; however some issues have not been addressed. We have provided suggestions concerning the questionnaire and the analysis plan, as discussed above.

Labeling

These comments are those of HFD-40, and do not necessarily represent a joint perspective with other divisions, as did the comments on the questionnaire. Further information will be sent to the sponsor to guide labeling revisions.

In the label that is in the Drug Facts Format, I suggest in the "Do Not Use" section, that the sponsor move "in girls less than 12 years of age" and "for external itching" to become bullets 2 and 3. That way, all warnings about who should not use the product appear before warnings about how to use it.

I suggest changing some words to simplify the language. Specifically, on the carton label, "experience" could be changed to "have" and "consult" could be changed to "talk to." On the insert, there are many opportunities to simplify the language. I would encourage the sponsor to substitute shorter words for longer ones and generally make the language easier to understand whenever possible.

On the directions for use, I suggest the following:

Step 3: Change "release" to "stop" Add a sentence at the end saying something such as "Turn the applicator to unscrew it and to separate it from the tube."

Step 4: I suggest adding a final sentence stating why tampons should not be used. It is more likely this instruction will be followed if women are given a reason for following it. A statement such as "Tampons may remove the medicine from the vagina" is suggested.

In the section on "For Best Results," under #4, I suggest simplifying "penile itching" to "itching of his penis." "Penile" is a word that may not be recognized by persons with low reading ability. Under #6, I suggest substituting "you use the toilet" instead of "a bowel movement or urination." Under #7, I suggest simplifying "disturb the vaginal bacterial balance" to something simpler, such as "cause the yeast to grow."

Advice should be included concerning use of vaginal products while using this medication and the advisability of vaginal intercourse, if appropriate.

To the extent possible, the label and insert should incorporate language and format

consistent with the agency's most recent thoughts about labeling for this class of drugs. This information should be transmitted to the sponsor if we determine it is appropriate. Additional labeling comments will be suggested by HFD-560 and HFD-590.

APPEARS THIS WAY
ON ORIGINAL

/S/

Karen Lechter, J.D., Ph.D.
Division of Drug Marketing, Advertising, and
Communications

APPEARS THIS WAY
ON ORIGINAL

Reviewer: Daniel Davis, M.D., M.P.H.
Division: Special Pathogens and Immunologic Drug Products, HFD-590
NDA#: 20-827
Sponsor: Advanced Care Products
Drug: Monistat 3 Vaginal Cream (miconazole nitrate 4%)
Date Submitted: November 17, 1997
Date Completed: February 25, 1998

Re: NDA # 20-827, Monistat Vaginal Cream (miconazole nitrate 4%- 3 day), sponsored by Advanced Care Products. On November 17, 1997, the agency received a revised Label Comprehension Study (LCS) from Advanced Care Products

The following medical officer comments reflect original ideas, and common concerns shared with Karen Lechter in HFD-40 and Ling Chin in HFD-560. The November 17th submission included Advanced Care Products' responses to the joint reviews provided earlier by the three divisions of the FDA. It also contained a revised protocol and questionnaire.

Methodology Issues:

1. There were comments concerning the potential use of two labels with one being a "control" or comparator label. It also appeared that the study would use flat paper copies of the carton label and the package insert (educational brochure).

MO Comment: recommend the use of only one carton label and one package insert, without a comparator, and that the new Drug Facts Format be used for the label. The agency is willing to help with the writing/editing of both the label and the insert. Strongly recommend that the actual package/box be used for this study as this is intended to be an OTC product, and in actual use women will be reading from the box and not from a flat piece of paper. Also recommend that the print size be exactly what is used on the actual product.

2. Mail recruitment: need to clarify actual # of sites and total # of participants as this was stated in the original proposal, but was not mentioned in the second proposal. What exact ranges and what specific methods will be used to "assure a population mimicking that of the U.S. population?"

MO Comment: This was discussed at the telecon on 1/16/98. The MO's final impression is that there will be 20 sites with 20 participants per site, and that a "quota system" will be used per site to help assure the desired target population.

3. ACP proposes a sample with ~25% of participants having ever suffered from a yeast infection.

MO Comment: A 12/25/97 review article in the NEJM by Jack Sobel, MD, states (p.1896) that "at least one episode of VVC (vulvo-vaginal candidiasis) is reported in up to 75% of premenopausal women." Furthermore, a 1997 vaginitis article in Infectious Diseases in Clinical Practice by Sherwood Gorbach, MD, states (p. 284) that "VVC occurs in 75% of women in their lifetime; 50% of women have two or more episodes." Based on this data and the fact that the product is intended for women with a prior proven vaginal yeast infection, the strong recommendation is that the above proposed percent should be at least 50%.

4. ACP states that "age will be requested in terms of ranges," but the questionnaire asks, "What is your age, please? _____ (YEARS)."

MO Comment: We recommend that an age range, and not an exact age, be used. The questionnaire should reflect this.

5. ACP wants this OTC product approved for "girls" age 12 and older, but the proposed study will sample only women >18 years of age.

MO Comment: Either the LCS should include a younger age range (12-18 years old), or the product should not be used by females < age 19, or the label should reflect some of the concerns (such as vaginitis misdiagnosis, sexual abuse, concurrent STDs, unsuspected pregnancy) inherent in very young females (especially ages 12 to 15) using this as an OTC product.

Analysis Plan Issues:

1. In Attachment 3 (Analysis Plan), the proposal used a guideline of "Objective Satisfied If: 80% and 50% correct ..." for specific questions.

MO Comment: The biometrics issue of setting cut off limits for the analysis of the data in this label comprehension study was discussed at the telecon on 1/16/98. The agency does not want to have a set limit for "correct responses," but recommends that each question should have an overall evaluation; certain "key" questions that are considered most important should probably have a "correct" answer a very high percentage of the time. Questions with a much lower "correct" answer rate may reflect a problem with either the question itself or the information on the label or insert. Appropriate changes could be made after the LCS is completed and analyzed.

Comments about the Questionnaire:

1. Too long as it is currently proposed.

MO Comment: Recommend that questions 16 through 26a be deleted as they are redundant and will not really contribute additional information to this LCS.

2. Simplify the language per Karen Lechter's many examples.

3. **MO Comments on specific questions:** the collective comments from the three divisions have been consolidated and incorporated in Karen Lechter's detailed review under suggestions for the questionnaire.

Carton Labeling:

The Drug Facts Format is much clearer and better than the old format. Consider changing, however, the following words (listed in order of their appearance on the carton) to simpler or more inclusive choices:

without a prescription	→ in prescription strength
antifungal	→ treat yeast
doctor	→ doctor/healthcare provider
before	→ in the past
interfere with	→ absorb some of

100° F	→ 100° F orally
experience	→ have
temporary	→ short-lived
consult	→ talk to
and bedtime)	→ (morning and <u>afternoon or evening</u>)
expiration	→ expiration
nursed staffed	→ nurse-staffed

The old format label is generally hard to read, has too much bolding and capitalization, and the print is too small. We do not recommend it be used in the label comprehension study.

Other General Labeling Issues:

1. The FDA is currently in the process of completely revising the carton label and package educational insert for VVC products, and would recommend that ideally the newer FDA-revised results be used by all products, both OTC and Rx, indicated for the treatment of VVC.

2. No advice is given about the concurrent use of vaginal products such as N-9, lubricating gels, feminine sprays, condoms, etc. Moreover, no advice is given about sexual activity surrounding the use of the product.

MO Comment: Recommend that such information should be on the label or insert, and that the Label Comprehension Study should test this information.

/S/

MD, MPH

Daniel Davis, MD, MPH
Medical Officer, DSPIDP
HFD-590

For concurrence only:
Mark Goldberger, MD, MPH
Brad Leissa, MD

cc:
ORIG NDA 20-827
HFD-590
HFD-590\Goldberger\Albrecht\Leissa\Davis\Winfield\Chi
HFD-560
HFD-560\Bowen\Katz\Chin\Walther
HFD-46
HFD-46\Lechter

Reviewer: Dan Davis, MD, MPH
Division: ODE IV, DSPIDP, HFD-590
NDA #: 20-827
Drug: Monistat Vaginal Cream (miconazole nitrate 4%)
Sponsor: Advanced Care Products
Study: Label Comprehension Study Protocol
Date Submitted: July 17, 1997
Date Completed: Sept. 4, 1997

MO Review: concerning the proposed Label Comprehension Study from ACP [redacted]
[redacted] These comments reflect original ideas, and
common concerns shared with Karen Lechter in HFD-40 and Ling Chin in HFD-560.

THE FORMAT:

The 20 sites and 400 women seems reasonable, but I recommend recruiting some subjects from sites such as supermarkets and pharmacies where women would actually go to buy this OTC product. The sample should include women who believe they currently have a vaginal yeast infection, and women of lower socio-economic environments and/or limited educational levels.

The large majority of the 400 women should have had a prior yeast infection as this OTC product should be used by women who have had at least one previous vaginal yeast infection. We really want to determine if women who are using the product can understand the label, use the product correctly, know when not to use the product, and when to appropriately seek further medical advice.

There should be a "comparator" package label and educational insert. Then there would be a means of evaluating this ACP Monistat label relative to a similar product. Eligible respondents should be given the actual boxed product to read (not a copy of the package labeling) as this will approximate the OTC setting. Likewise, the educational brochure insert should be the folded insert identical to the actual insert. Part of comprehending a label is the ability to read it "as is."

THE QUESTIONS:

Item #4: after first instructing the woman to read the product label, ask a limited number of questions to evaluate some general concepts such as:

1. For whom is this product intended?
2. How many days is the product used?
3. How soon can you expect relief of your symptoms?
4. What are the chances it will cure your infection?
5. How safe is it?

Items #5-14: ask this set of more detailed questions with the respondents being allowed to re-read the package label or refer back to the boxed product with more time to answer the questions.

In general, the questions are far too leading. The study asks only questions that can be answered by the label. It does not ask anything about information that is not covered, and it does not ask questions about meaning. I would add some questions (using the various styles discussed by Karen Lechter) covering the following topics:

1. Who should and should not use this product?
2. Does the label tell you what the chances are that this product will cure your yeast infection? (avoid the word "percent" in this question)
3. Can this product be used while you are having your menstrual period?
(Yes/ No/ Doesn't say/ I don't know)
4. What does the label say about using tampons, pads and mini-pads while using the product? (OK/ Not OK/ Doesn't say/ I don't know)
5. What does "cures most vaginal yeast infections" mean to you?
6. What does "full prescription strength" mean to you?
7. What does "consult your doctor" mean to you? (Phone the doctor right away? See the doctor within a week? Go to the nearest ER today? Talk with a nurse or healthcare provider in the doctor's office as soon as possible? Call or check with your local pharmacist? Etc.) Both the words "consult" and "doctor" may mean very different things to individual people.

My general comments and suggested changes relate to the choice of words and the form or content of the questions. Items 5 through 14 simply ask for the respondent to repeat the information on the package label back to the interviewer. This is not a strong test of label comprehension. A better test, for example, would be to ask the following:

- For item 7: "When and how is this product used?" The unspoken question is really: how often, what time of day, and internal versus external use. Record what the respondent says to ascertain how well she comprehends the label and the intended information in the label.
- For item 9: "When should this product not be used?" Furthermore, "What does the term 'signs or symptoms' mean?" Many people may not know, especially the term "signs."
- For item 10: "How soon should you notice improvement (feel better) when using this product?" "What should you do if you do not feel better?"
- Item 14 asks about the actual product use, but does not seem to acknowledge the obvious differences between internal and external use. For 14c., a third possible response is "The label is not clear about this question."

Items 17 through 26 concern the information in the package insert (educational brochure). The answers to these questions are not as easy to locate because of the format and length of the educational brochure, but I would ask the questions in a different form in many cases (please see Karen Lechter's comments). I would also add three questions

(although the brochure does not answer the questions), because the package insert should contain enough information to answer these questions:

- What does the educational brochure say about having sexual relations while using the medication?
- What is said about using the medication during your period?
- Why should you not use tampons while using the medication?

It would also be potentially very valuable to the sponsor to ascertain exactly how much time women actually spend looking at the choice of OTC products for VVC and reading their package labeling in the real-life setting of the supermarket or pharmacy. This information may influence the design and content of the package (box) label.

SUMMARY:

I would recommend many changes to the proposed Product Label Comprehension Study so that it would better test the meaning of the information to the respondent as well as the content (what it does and does not say). I also strongly endorse Ling Chin and Karen Lechter's general recommendations:

- State specific communication objectives
- Include a comparator label and insert
- Use a scenario format to ask some of the questions
- Use a checklist type of question in certain cases
- Use a limited number of open-ended questions (see Karen's precautions)
- Ensure inclusion of women with low literacy levels; simplify the language
- Develop a Drug Facts Format label for the product
- Be sure important health education information about vaginal yeast infections is included in the label and/or the insert

/s/ *MD, MPH*

Daniel Davis, MD, MPH
Medical Officer, DSPIDP

For concurrence only:

Mark Goldberger, MD, MPH
Brad Leissa, MD

cc:

ORIG NDA 20-827
HFD-590
HFD-590\Goldberger\Albrecht\Leissa\Davis\Chi
HFD-560
HFD-560\Bowen\Katz\Chin\Walther
HFD-46
HFD-46\Lechter

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 25, 1998
FROM: Christina H. Chi, Ph.D. */S/ 3/25/98*
SUBJECT: Safety update of NDA 20-827 Monistat 3 Vaginal Cream
TO: The NDA file

There is no safety update to this original NDA because all clinical studies were complete at the time of submission and therefore, without any ongoing clinical studies, there was no updated safety information to be submitted.

APPEND THIS WAY
ON ORIGINAL

Mar 20, 1998

Re: Consult for CDER on new formulation of Monostat-7 effect on latex condoms

Mike
Mike:

I've looked thru your draft review, with a focus on your conclusions. A few questions:

- My main thought is that it ought to be more than adequate if Ortho used the validation testing approach given in our expiration dating reg. I'm also concerned that we're asking for permeability data from Ortho when we don't ask condom latex mfrs to do the same.

Even using the expiration dating reg as a template, you need to examine why you're asking for three separate lots of condoms. This data is not supporting the performance of the condom; rather, it is looking at the effect of the Monostat-7 on the condom. Having additional lots of condoms does not really add anything to the picture.

On the other hand - as you mention - choosing a representative latex condom (or condoms) for testing is important. Ortho should make this choice in a way that best illustrates the potential effect of the Monostat-7 on the condom. It's not really a question of how many different kinds of condoms. Otherwise, we're going to be asked: Why is it necessary to test more than 3 different condoms? How many more? How do you choose? There is no one right answer to these questions. Rather, Ortho could be asked to justify why it chose the Lifestyles and Trojans condoms. Likewise, we should be asking ourselves why are these three condoms not a good test case for what Ortho is trying to establish: that the Monostat-7 does not significantly affect the latex condom.

- You mention that the data shows a decrease in airburst pressure, force-to-break, tensile strength, and elongation of the "treated" condoms compared to their controls. You need to look at how much each of these parameters decreased and whether that has any real meaning in the context of the condom use. Are these dramatic decreases or minor? Do the condoms still fall within standard boundaries? Again, there is no obligation to strictly adhere to each and every sampling requirement of the standard to answer some of these questions. Rather, you are asking whether these observed trends have any real meaning in the context of a woman using Monostat-7 and her partner using a latex condom.

There's no "standard", *per se*, that you can use to answer this question. The ASTM and ISO standards were not developed to answer this question, and neither was the expiration dating reg. It's an issue of using our scientific judgment, based on our experience with condoms, latex, and testing. What testing regimen do condom mfrs use to "screen" materials that may or may not be used with latex or polyurethane condoms?

Depending on whether the differences are great or not, I would like to know how (or if) Ortho plans to address this in the labeling.

Anyway, that's my basic take on this issue. Let's get together and discuss in greater detail, form a plan to reach closure. If it's helpful, we can involve Dr. Chi.

/S/

CDER Establishment Evaluation Report
for March 25, 1998

Application: NDA 20827/000
Stamp: 31-MAR-1997 Regulatory Due: 31-MAR-1998
Applicant: ADVANCED CARE PRODS
691 US RT 1 SOUTH
NORTH BRUNSWICK, NJ 08902

Priority: 3S
Action Goal:
Brand Name: MONISTAT 3 VAGINAL CREAM
(MICONAZOLE NIC)
Established Name:
Generic Name: MICONAZOLE NITRATE
Dosage Form: EMC (EMULSION, CREAM)
Strength: 4.0% CREAM (200 MG DOSE)

Org Code: 590

District Goal: 29-NOV-1997

FDA Contacts: C. CHI (HFD-590) 301-827-2125 , Project Manager
D. MATECKA (HFD-590) 301-827-2398 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

ACCEPTABLE on 06-FEB-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 02-OCT-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
Milestone Date 06-FEB-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
Milestone Date 05-FEB-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No: [redacted]
[redacted] AADA No:

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER

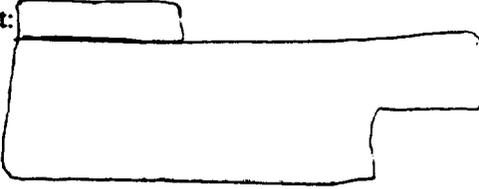
CDER Establishment Evaluation Report
for March 25, 1998

Page 2 of 2

DRUG SUBSTANCE PACKAGER

Milestone Date 12-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:



DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 02-OCT-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
 MANUFACTURER
 FINISHED DOSAGE PACKAGER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: (Division/Office) **DRH, HFD 470**
 FROM: **ODE IV**
CD2R, HFD 590.
 Feb 19, 1998 IND NO. NDA NO. 20-827 TYPE OF DOCUMENT **original NDA** DATE OF DOCUMENT **March 31, 1997**

NAME OF DRUG **Momistat 3 Vaginal Cream** PRIORITY CONSIDERATION **Top priority please** CLASSIFICATION OF DRUG **Vaginal Drug Product Therapeutic: Antifungal** DESIRED COMPLETION DATE **March 31, 1998**
 NAME OF FIRM **Advanced Care Products** **NDA due date Mar. We appreciate ASAI Please call 827-218 the consult pick-up**

REASON FOR REQUEST

I. GENERAL

- | | | |
|---|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input checked="" type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input checked="" type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (Specify below)
<i>New formulations of the base cream for a new cream</i> |
| <input type="checkbox"/> MEETING PLANNED BY _____ | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER |
| <input type="checkbox"/> OTHER | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> BIOPHARMACEUTICS | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL PRECLINICAL

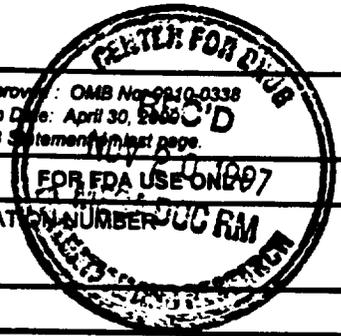
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

Please review the report **PD-R-0420-1**
Compatibility of Miconazole Nitrate (4.0%) Vaginal Cream with **Commercial Latex Condoms**

SIGNATURE OF REQUESTER: **/S/ Norman SCHMUFF, HFD 590 (590)** METHOD OF DELIVERY (Check one): MAIL HAND
 SIGNATURE OF RECEIVER: **/S/** SIGNATURE OF DELIVERER: **/S/** DATE: **2/19/98**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
 ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0338
 Expiration Date: April 30, 2005
 See OMB Statement on next page.



APPLICANT INFORMATION

NAME OF APPLICANT Advanced Care Products		DATE OF SUBMISSION 11/19/97	
TELEPHONE NO. (Include Area Code) (732) 524-1676		FACSIMILE (FAX) Number (Include Area Code) (732) 524-1344	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): PO Box 6024 691 Highway 1 South North Brunswick, New Jersey 08902		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) NDA 20-827			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) miconazole nitrate, USP		PROPRIETARY NAME (trade name) IF ANY MONISTAT® 3 Vaginal Cream	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 1-[2,4-dichloro-(2,4-dichlorobenzoyloxy) phenethyl] imidazole nitrate			CODE NAME (if any)
DOSAGE FORM: cream	STRENGTHS: 4.0% per 100 mg dose	ROUTE OF ADMINISTRATION: Intravaginal/topical	
(PROPOSED) INDICATION(S) FOR USE: Over-the-Counter 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 APPLICATION (ANDA, AADA, 21 CFR 314.64)	
<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)	<input type="checkbox"/> 507
IF AN ANDA, OR AADA, 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"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

REASON FOR SUBMISSION			
Information was inadvertently omitted from 11/18/97 submission			

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 checked="" type="checkbox"/> PAPER	<input type="checkbox"/> PAPER AND ELECTRONIC	<input type="checkbox"/> ELECTRONIC
--------------------------------------	---------------------	---	---	-------------------------------------

ESTABLISHMENT INFORMATION			
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)			

See Attached

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>	Form Approved: OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on last page.
	FOR FDA USE ONLY
	APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Advanced Care Products, Personal Products Company	DATE OF SUBMISSION 01/29/98
TELEPHONE NO. (include Area Code) 732-524-1675	FACSIMILE (FAX) Number (include Area Code) 732-524-1344
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 691 Route 1 South P.O. Box 6024 North Brunswick, New Jersey 08902 USA	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) NDA 20-827		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) miconazole nitrate, USP	PROPRIETARY NAME (trade name) IF ANY MONISTAT 3 Vaginal Cream	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) <small>1-(2,4-dichloro-ft-(dichlorobenzyl)oxy) phenethyl imidazole nitrate</small>	CODE NAME (if any)	
DOSAGE FORM: Cream	STRENGTHS: 4.0% cream, 200mg dose	ROUTE OF ADMINISTRATION: Intravaginal
(PROPOSED) INDICATION(S) FOR USE: Over-the-Counter 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 APPLICATION (ANDA, AADA, 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)		
<input type="checkbox"/> 507		
IF AN ANDA, OR AADA, 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"/> EFFICACY SUPPLEMENT		<input type="checkbox"/> LABELING SUPPLEMENT	
<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT		<input type="checkbox"/> SUPAC SUPPLEMENT	
<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT		<input type="checkbox"/> OTHER	

REASON FOR SUBMISSION
 Submission of Mock Up Draft Labeling

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx) OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 **THIS APPLICATION IS**

PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

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, 610(k)s, IDEs, BMFs and DMFs referenced in the current application)

see Attached

NDA 20-827
Miconazole Nitrate (4.0%) Vaginal Cream
Expected Introduction Calculation (EIC)

The following equation is taken from "Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplement", November 1995.

$$\text{EIC-Aquatic (ppm)} = A \times B \times C \times D$$

Where A = kg/year production
 B = 1/liters per day entering POTW's*
 C = year/365 days
 D = 10^6 mg/kg (conversion factor)

* 1.115×10^{11} liters per day entering publicly owned treatment works (POTW's),
Source: 1992 Needs Survey, Report to Congress, Spetember 1993, EPA 832-R-93-002

$$\text{EIC-Aquatic (ppm)} = A \times B \times C \times D$$

Where A = 11238 kg/year production - for year 5 (all dosage forms and strengths)
 B = $1/1.115 \times 10^{11}$ liters/day
 C = year/365 days
 D = 10^6 mg/kg

$$\text{EIC-Aquatic (ppm)} = .276 \times 10^{-3}$$

$$\text{EIC-Aquatic (ppb)} = .276$$

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 21, 1997
Time: 4:30 - 5:10 PM
Location: 9201 Corporate Blvd.,
Rockville, MD. 20850

Application: NDA 20-827 Monistat® 3 Vaginal Cream
miconazole nitrate 4%

Type of Meeting: 45-day filing meeting

Meeting Chair: Christina Chi

Meeting Recorder: Christina Chi

Attendees: Division of Over The Counter Drug Products:
Debra Bowen, M.D., Division Director
Rosemary Cook, Supervisory Project Manager
Helen Cothran, Team Leader
Sakineh Walther, R.N., Project Manager

Division of Special Pathogen and Immunologic Drug Products:
Mark Goldberger, M.D., Act. Division Director
Brad Leissa, M.D., Medical Team Leader
Joseph Winfield, M.D., Medical Officer
Daniel Davis, M.D., Medical Officer
Norman Schmuff, Ph.D., Chemistry Team Leader
Sherry Lard, Ph.D., Supervisory Microbiologist
Linda Gosey, Microbiologist
Owen McMaster, Ph.D., Pharmacologist
Chandra Sahajwalla, Ph.D., Biopharmaceutics Team Leader
Nancy Silliman, Ph.D., Act. Supervisory Statistician
Cheryl Dixon, Ph.D., Statistician
Christina Chi, Ph.D., Project Manager

Division of Drug Marketing, Advertising, and Communication:
Karen Lechter, Ph.D., J.D., Social Science Analyst

Completed fileability checklist supplied by:

Ling Chin, M.D., Medical Officer, OTC
Phil Colangelo, Ph.D., Biopharmaceutics, DSPIDP
Dorothy Matecka, Ph.D., Chemistry, DSPIDP

Background:

1. This is an application of a vaginal drug product to treat recurrent vaginal yeast infection (candidiasis) received by DAIDP/DSPIDP since the establishment of MAPP which is intended for a direct OTC marketing. In accordance with MAPP 6020.5-B-2, a bi-divisional meeting was convened on May 21, 1997. A review team was formed and a general review plan was set. Clinical reviewers of both OTC (Dr. Ling Chin) and DSPIDP (Dr. Daniel Davis) discussed splitting the review responsibilities.
2. The active ingredient of this product has been used in several approved products in this country and abroad for both prescription and OTC marketing, but this application is the first and only vaginal cream with a 4% miconazole nitrate (200 mg miconazole nitrate) dosing regimen per day. This dosing regimen is similar to the OTC approved (April 16, 1996) Monistat® 3 Combination Pack with a 200 mg miconazole nitrate suppositories and the Rx approved (Aug 15, 1994) Monistat® 3 Suppositories with 200 mg miconazole nitrate.

Meeting Objectives:

1. To determine the fileability of NDA 20-827 Monistat® 3 Vaginal Cream.
2. To decide clinical and labeling review assignments between DSPIDP and OTC.
3. To discuss the necessity of calling an Advisory Committee.
4. To ascertain which Division will sign off the letter.

Discussion Points:

- | | |
|-----------------------|---|
| 1. Chemistry: | Fileable. |
| 2. Pharm./Toxicology: | Fileable. |
| 3. Microbiology: | Fileable. |
| | Sponsor will be asked to respond to some questions. |
| 4. BioPharmaceutics: | Fileable. |
| 5. BioStatistics: | Fileable. |
| 6. DDMAC: | Fileable. |
| 7. OTC: | Fileable. |
- Dr. Chin to review the safety of the product.
- * Clarification of the final formulation and composition difference between this proposed 4% cream and the approved 2% cream will be requested from the sponsor.
 - * Carcinogenicity data was not found.
 - * Concerns about inadequacy of exposure time to women (no prescription history) was expressed.
 - * If a safety concern is found, presentation to a joint Advisory Committee will be recommended.

* A set of Clinical Reviewer's copy, the overseas marketing safety data, and a sampling of foreign labeling (translated into English) for both the prescription and OTC marketing should be requested from the sponsor.

8. DSPIDP:

Fileable.

* Dr. Davis to review the efficacy of the product.

* Since almost 10% of data in one of the pivotal studies was done in Costa Rica, more information should be requested to justify applicability to US population.

Decisions (agreements) reached:

1. The application is fileable.
2. The clinical review responsibilities will be shared by both Divisions.
*Dr. Chin will do the clinical safety review;
*Dr. Davis will take care of the efficacy review.
3. The labeling review responsibilities will be shared by both Divisions.
4. The letter will be signed off by both the OTC and DSPIDP Directors.
5. Monthly progress meetings for reviewers and project managers will be held.

Unresolved issues or issues requiring further discussion:

1. Is this 4% cream in the lesser (old) or the more viscous (new) composition?
2. Since the applicant requests direct OTC marketing, could a label-comprehension study be suggested?

Action Items:

<u>Item</u>	<u>Responsible Person</u>	<u>Time Frame</u>
1. Composition/viscosity	Dr. Schmuff	ASAP
2. Micro questions	Drs. Gosey & Chi	ASAP
3. Clin. Rev.'s jackets for OTC	Chi	ASAP
4. Request to DSI (Dr. Thomas)	Drs. Davis & Chi	ASAP
5. Overseas marketing safety data	Chi	July 1, 1997