CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

CORRESPONDENCE

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

March 30, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate cream)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, submitted on March 31, 1997. Reference is also made to the conversation with teleconference of 3/30/98 between, Food and Drug Administration and Advanced Care Products on 3/30/98.

We commit to submitting 20 copies of Final Printed Labeling that are identical to the draft labeling submitted 3/27/98 with the following revisions:

1. The generic name will be stated as "miconazole nitrate cream".

2. We will use the spelling of "gray" instead of "grey" within our Directions For Use section of the Educational Brochure.

3. We agree to provide the recumbent position as the second illustration within the Directions For Use section of the Educational Brochure.

4. The trade name for this product will be "MONISTAT 3 Vaginal Cream".

5. In the last sentence within the "What Is A Vaginal Yeast Infection (Candidiasis)" paragraph we will remove the word "at" which precedes the CDC phone numbers.

We also commit to conduct a label comprehension study as a Phase IV study, to be completed within one year of this product's approval.

Advanced Care Products
NDA 20-827
MONISTAT 3 Vaginal Cream
(miconazole nitrate cream)
Letter of Commitment
March 30, 1998

We request that this Letter of Commitment be made part of Original NDA 20-827. Should you have any questions or need additional information, please contact me directly at 732-524-1675.

Sincerely,
ADVANCED CARE PRODUCTS

Rhea N Williams for

Diane Herron
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: April 14, 1998

/S/ 11/16/99 Ph.D.

From: Christina Chi, Ph.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: NDA 20-827: Monistat®3 Vaginal Cream (Miconazole Nitrate 4% cream)
Compatibility and Use with Latex Condoms

To: Advanced Care Products
691 Highway 1
North Brunswick, New Jersey 08902-0724

Background: ACP [redacted] to conduct a condom and diaphragm compatibility study with the new base formulation miconazole nitrate cream (4%). The results of this study were submitted to NDA 20-827. The testing included three latex condom brands, Trojan-Enz Lubricated, Trojan-Enz Non-Lubricated, and Lifestyles Ultra Sensitive Non-Lubricated. Each test condom was compared with non-treated condoms. Testing was carried out by standard methods for both airburst pressure and volume, and tensile properties (thickness, break force and tensile strength, and elongation %).

We would like to communicate the following comments to you:

- There was little difference between the treated and untreated Trojan brands; there was, however, a general trend toward a decrease in the different measured properties.

- With the Lifestyles brand condom there was a statistically-significant decrease in airburst pressure, and in the tension properties of force to break, tensile strength, and elongation. The burst volume was the only property that was not affected, but the slight increase in the volume may indicate a softening of the material following treatment with the miconazole nitrate (4%) cream.

- The statistically-significant decrease in the stress and strain properties of the Lifestyles latex condom may represent a detrimental finding with this condom formulation. However, the results show that following treatment with the miconazole nitrate (4%) and under the conditions of the test, the Lifestyles condoms would pass the current voluntary standard (minimum values) for latex condoms for each test measure.

- The condom study used standard testing methods, but did not test for the worst case stress conditions, and did not test the barrier or permeability properties of the condoms.

- Only 3 types of condoms, and only one lot of each brand were tested. It is extremely difficult to extrapolate these results to all legally-marketed condoms. In fact, the effect on a differing formulation of latex was seen in the test with the Lifestyles condom compared to the two tested Trojan Brands.

In conclusion, we believe that ACP has not provided sufficient data to demonstrate that the new base formulation Monistat® cream will not adversely affect the physical integrity of latex contraceptive condoms. The physical properties of the latex condoms exposed to Monistat®3 Vaginal Cream appeared to decrease for both brands of latex condoms. Most significantly, the one lot of Lifestyles Condoms compared to controls showed statistically-significant decreases in strength characteristics. Whether or not these differences have clinical significance were not addressed by ACP in their submission. Nevertheless, Monistat®3 Vaginal Cream does appear to have some physical effects on latex condoms under the conditions tested, and there remains some doubt that the new formulation is safe for use with all latex condoms.

Recommendation:

- That the product continue to include a caution about reliance on condoms, diaphragms and other contraceptives made of latex for prevention of pregnancy or other STDs:
  "Do not rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy while using Monistat® 3 Vaginal Cream."

- If ACP wants to further pursue the deletion of the condom/diaphragm warning, the Agency recommends the following issues be addressed by ACP as a labeling supplement:

  a) Discussion of the adverse test results; specifically, what is ACP's assessment of the statistically-significant decreases in the strength properties of the test condoms compared to the controls?

  b) Additional testing of other manufacturers' condoms or justification by the applicant for why they chose the Lifestyles and Trojans condoms for the study.

  c) How can these data be utilized to rule out possible Monistat® 3 induced changes in latex permeability?

  d) Does Monistat® 3 adversely affect spermicides?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: February 25, 1998

To:

From: Dorota Matecka, Ph.D., Chemistry Reviewer DM. 2/25/98

Through: Norman R. Schmuff, Ph.D., Chemistry Team Leader NRS 2/25/98
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: CMC Comments/Type II DMF (Miconazole nitrate, Drug Substance)

With regards to your 1/29/98 submission addressing FDA questions, please address the following CMC comments:

1. The response to question #2 states that the miconazole nitrate manufacturing process "...is well-controlled with the temperature ranges, reaction/drying times and pH controls...". Please describe the details of these controls.

2. Please lower the specifications from in the specifications for the drug substance, miconazole nitrate. Based on the certificates of analysis results for the three batches of miconazole nitrate and the stability results for the According to the ICH Guidelines, Q3A, "...where is no safety concern, impurity specifications should be based on data generated on actual batches of the new drug substance allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the new drug substance."

3. Please submit a new, revised stability protocol for the drug substance, stated to be uniform manufacturing sites. Please commit to use the HPLC method to measure the levels of individual and total impurities, during the course of stability testing.

Also, please address the further questions regarding the [redacted]

1. How long is the product (miconazole nitrate, [redacted]? How is the content of organic solvents [redacted] ontrolled in the final product? Please include the specification for the residual solvents in the specifications for the drug substance, miconazole nitrate.

2. For the rework procedure, please provide details of when this process would be done. Also, please provide acceptance criteria for a satisfactory rework.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date February 19, 1998

From Dorota Matecka, Ph.D., Chemistry Reviewer, HFD-590, CDER D.M. 2/19/98

Subject CMC comments regarding NDA 20-827, Monistat 3 Vaginal Cream

To Diane Herron,
Director, Regulatory Affairs
Advanced Care Products

Please address the following CMC comments regarding the NDA 20-827 (Monistat 3 Vaginal Cream):

1. Please revise the specifications for the drug substance to conform with the specifications for Miconazole Nitrate included in the Type II DMF [redacted]

2. Please submit the documentation from statistical analysis studies performed on at least three commercial-size NDA stability batches. Confirm that the longest period of the stability testing at [redacted] is 12 months for one batch [redacted] (3 months for the other two batches [redacted]). The stability data submitted in the NDA for the drug product do not support the requested expiration dating of 36 months.

3. Based on the stability results (both initial testing and on storage) it appears that the highest total [redacted] (of the miconazole nitrate peak area) for the sample stored for 3 months at [redacted]. In the specifications for the drug product, please lower the limit for total impurity from [redacted]

4. Please include a specification for Combined Yeasts and Molds Count as "max. 10 cfu/g" in the drug product specifications for microbial limit to conform to the recommended values in the recent PF (Vol. 22, No. 6, p. 3102, Table 1. Assignment of Microbial Limit for Nonsterile Dosage Forms, According to Route of Administration). A specification of no Candida albicans should also be set for the drug product.

5. What are the detection limits and extractable levels of the extractables from the rubber plunger component of the Miconazole Nitrate 4.0 % Vaginal Cream prefilled applicators? Please explain the discordant results in the level of [redacted] reported at the same conditions for the same lots (i.e. [redacted] in Table 1 (p. 03-000210, vol. 1.2) and Table XIV (p. 03-000427, vol. 1.3), respectively.

Date: October 30, 1997

To: Advanced Care Products
P.O. Box 6024
691 U.S. Route 1 South
North Brunswick, New Jersey 08902
Fax # 908-524-1344
Att: Ms. Diane Herron

From: Dorota Matecka, Ph.D.
Chemistry Reviewer

Through: Norman R. Schmuff, Ph.D. /S/ 10/30/97
Chemistry Team Leader
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: Environmental Assessment / NDA 20-827

Please, address the following comment regarding the Environmental Assessment Information submitted with your NDA 20-827:

The EA for NDA 20-827 is deficient with regards to the Expected Introduction Concentrations (EIC). As described in the July 29, 1997 Federal Register / Vol. 62, No. 145 and as cited in the November 1995 CDER "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements", Section III. D. 6 e. page 13, the EIC "...should be based on the total fifth year production estimates for all dosage forms and strengths included in the application or related (companion) applications." Please, calculate the EIC based on the ENTIRE miconazole nitrate product line and use that to determine if this application qualifies for a Tier 0 EA. Please, refer to the previously cited FR notice for further information.

If you have any questions, please feel free to contact me at 301-827-2175 or Nancy Sager, Environmental Assessment Team Leader, 301-594-5629.

/S/

Dorota Matecka, Ph.D.
Review Chemist, HFD-590

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

March 25, 1998

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-827
MONISTAT 3 Vaginal Cream

Dear Dr. Chi:

Reference is made to our submission of mock-up labeling of January 29, 1998. At this time we wish to withdraw the coupons found on the Educational Brochure. In addition, we confirm our commitment that, we will not print coupons on our Education Brochure in the future.

We hope this satisfies your concerns regarding the use of coupons on our product labeling. Please let me know if you need additional information.

Very Truly Yours,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Not Send to Archive Yet

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

March 25, 1998

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-827
MONISTAT 3 Vaginal Cream

Dear Dr. Chi:

The purpose of this letter is to confirm our commitment that, during April 1998 we will submit a Miconazole Nitrate Vaginal Cream monograph for inclusion in the United States Pharmacopeia (USP).

We hope this satisfies your concerns regarding the name of our product. Please let me know if you need additional information.

Very Truly Yours,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

post mend - a.chi.c gw

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

March 25, 1998

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-827
MONISTAT 3 Vaginal Cream

Dear Dr. Chi:

Reference is made to our submission of mock-up labeling of January 29, 1998. At this time we wish to withdraw the coupons found on the Educational Brochure. In addition, we confirm our commitment that, we will not print coupons on our Education Brochure in the future.

We hope this satisfies your concerns regarding the use of coupons on our product labeling. Please let me know if you need additional information.

Very Truly Yours,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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

BB. (SNC) orig. amendment Hand to date: 3/6/98.

Personal Desk Copy

March 5, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, submitted on March 31, 1997. Reference is also made to the conference call with Dr. Chin and Dr. Davis, Food and Drug Administration, and Rhea Williams, Fred Cone, Cathy Lamia and Josephine Harley, Advanced Care Products on 2/19/98. Reference is also made to the 2/18/98 conversation between Dr. Chin and Diane Herron, Advanced Care Products. On these two occasions, Dr. Chin asked questions regarding the review of the safety information.

As requested by Dr. Chin, we are submitting statistical analyses of the distribution of adverse experiences in the two pivotal studies of miconazole nitrate 4% vaginal cream. In addition, we have enclosed the responses regarding: the MONISTAT "old base" being used in the clinical studies submitted to NDA 20-827, the 822 adverse drug reports referenced in the safety data for worldwide experience and the 46 cases cited in the LANCET "letter to the editor".

Dr. Chin also requested the month and year that MONISTAT 7 Vaginal Cream, new base formulation was launched. This occurred in November, 1997.

We request that this information is made part of NDA 20-827 and we trust that you will find this submission satisfactorily addresses the questions as communicated to us by Dr. Chin. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,
ADVANCED CARE PRODUCTS

Rhea N. Williams for

Diane Herron
Director, Regulatory Affairs

CC: Dr. Chin

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

February 24, 1998

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

PERSONAL DESK COPY

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Chi:

As per your conversation with Diane Herron, Advanced Care Products, on February 24, 1998, enclosed please find two desk copies containing a Microsoft Word version of the draft labeling submitted in our pending New Drug Application, NDA 20-827 MONISTAT 3 Vaginal Cream.

When we submitted a mock up version of the draft labeling, the "Questions" section on the Folding Carton and Educational Brochure was updated to clarify the hours of operation for Advanced Care Products answer line. Therefore, this Microsoft Word version has been updated accordingly. The labeling for the Folding Carton and Educational Brochure for the Reusable and Disposable Applicators has been deleted from this file since we withdrew these put-ups from consideration at this time.

A listing of the file names found on each diskette for the draft labeling has been enclosed. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,
ADVANCED CARE PRODUCTS

Rhea N. Williams for

Diane Herron
Director, Regulatory Affairs

3/3/98 2 disks - 1 D. Davis
1 B. Lewis

Enclosed

Extra Cpy

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

February 19, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to a Pending Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversation that occurred on February 18, 1998 between Dr. Christina Chi and Dr. Dorota Matecka, Food and Drug Administration and Diane Herron, Advanced Care Products. The conversation focused on the lack of documentation supporting the use of a reusable and disposable applicator with MONISTAT 3 Vaginal Cream.

This information was inadvertently not included in our Pending Application, NDA 20-827, although we did provide technical information for a 25 gram tube. We respectfully withdraw from consideration the following MONISTAT 3 Vaginal Cream put-ups: MONISTAT 3 Vaginal Cream with 1 Reusable Applicator and MONISTAT 3 Vaginal Cream with 3 Disposable Applicators. We understand that MONISTAT 3 Vaginal Cream Prefilled Applicators is the only put-up under consideration for NDA 20-827. We further understand that the tube information will remain as part of our NDA, but the tube put-up will not be marketed until the disposable and reusable applicators are approved. We intend to submit a supplemental application requiring prior approval to provide for the Reusable and Disposable applicators at a later date.

We request that this information is made part of NDA 20-827 and we trust that you will find this submission satisfactorily addresses the issues as communicated to us by Dr. Matecka. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

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

NC
NEW CORRES.
ORIGINAL

February 19, 1998

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Chi:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. As you requested, we are sending two additional copies in mock form of the draft labeling for the MONISTAT 3 Vaginal Cream Prefilled Applicator put-up submitted to NDA 20-827.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Rhea N Williams for

Diane Herron
Director, Regulatory Affairs

Enclosed

APPEARS THIS WAY
ON ORIGINAL

BC. Mif amendment
received CDER Feb 20, 1998

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

February 19, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to a Pending Application
Withdrawal of disposable & reusable applicators
NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversation that occurred on February 18, 1998 between Dr. Christina Chi and Dr. Dorota Matecka, Food and Drug Administration and Diane Herron, Advanced Care Products. The conversation focused on the lack of documentation supporting the use of a reusable and disposable applicator with MONISTAT 3 Vaginal Cream.

This information was inadvertently not included in our Pending Application, NDA 20-827, although we did provide technical information for a 25 gram tube. We respectfully withdraw from consideration the following MONISTAT 3 Vaginal Cream put-ups: MONISTAT 3 Vaginal Cream with 1 Reusable Applicator and MONISTAT 3 Vaginal Cream with 3 Disposable Applicators. We understand that MONISTAT 3 Vaginal Cream Prefilled Applicators is the only put-up under consideration for NDA 20-827. We further understand that the tube information will remain as part of our NDA, but the tube put-up will not be marketed until the disposable and reusable applicators are approved. We intend to submit a supplemental application requiring prior approval to provide for the Reusable and Disposable applicators at a later date.

We request that this information is made part of NDA 20-827 and we trust that you will find this submission satisfactorily addresses the issues as communicated to us by Dr. Matecka. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

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

ORIGINAL

February 5, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, submitted on March 31, 1997. Reference is also made to the fax on December 31, 1997 from Christina Chi, Food and Drug Administration [redacted] The fax documented questions from the Chemistry reviewer regarding Janssen's Type II DMFs, [redacted] for Miconazole Nitrate Drug Substance and [redacted]. Janssen amended these DMF's to provide for the responses to the reviewer's questions; the response to DMF [redacted] was amended to that DMF on 1/28/98 and the response for DMF [redacted] was amended to that DMF on 1/30/98.

As requested by Dr. Chi, we are submitting this information to be made part of NDA 20-827 MONISTAT 3 Vaginal Cream, in an effort to document that the Chemistry Reviewer's questions have been addressed. We have also provided a copy of the responses for reference only because the respective DMF applications are the official source for this information.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Regards,
ADVANCED CARE PRODUCTS

Diane Herron
Director, Regulatory Affairs

Enclosure

Cc: Dr. Christina Chi (w/o attachments)

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

ORIG AMENDMENT

ORIGINAL

February 5, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, submitted on March 31, 1997. Reference is also made to the conversation between Dr. Christina Chi and Dr. Philip Colangelo, Food and Drug Administration, and Diane Herron, Advanced Care Products. Dr. Colangelo requested ACP perform a literature search on miconazole metabolism and examine the KI and KM's effect on Cytochrome P-450.

As requested by Dr. Colangelo, we are submitting a research report that documents the effect of imidiazoles on mammalian Cytochrome P-450 Enzymes. In addition, we have provided four bibliographies obtained through literature searches. The literature searches were conducted in the following databases for published and unpublished reports: Medline, Embase, CA Search

We respectfully request this information to be made part of NDA 20-827 MONISTAT 3 Vaginal Cream. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Regards,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

Enclosure

Cc: Dr. Christina Chi, Dr. Philip Colangelo

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

January 21, 1998

Dr. Christina Chi
Center for Drug Evaluation and Research (HFD-520)
Food and Drug Administration, Room S357
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Chi:

As discussed in our conversation on 1/21/98, enclosed please find two desk copies of computer diskettes containing the exact Microsoft Word versions of the draft labeling from Item 4c, beginning on p. 04-000101, in our Original New Drug Application, NDA 20-827 MONISTAT 3 (miconazole nitrate 4.0%) Vaginal Cream, submitted March 31, 1997. A listing has been enclosed which provides the file names for the draft labeling found on the diskette and the corresponding locations within the original application.

We have not provided FDA with an Archive Copy since this does not contain any new information. Please let me know if this meets your requirements.

The computerized version of the draft labeling is being provided to facilitate the review of our NDA 20-827.

Should you have any questions or need additional information, please contact me directly at 732-524-1675.

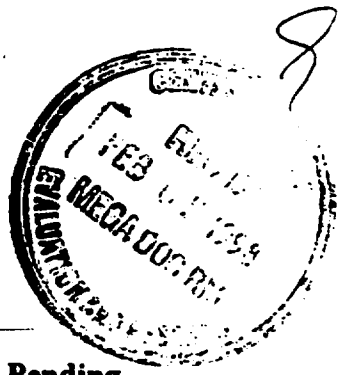
Sincerely,

ADVANCED CARE PRODUCTS

Kathy A. Mallet for

Diane Herron
Director, Regulatory Affairs

Advanced Care Products
Personal Products Company, Division of McNeil-PPC, Inc.
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724



January 29, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversation that occurred on January 23, 1998 between Dr. Christina Chi, Food and Drug Administration and Rhea Williams, Advanced Care Products. In this conversation, Dr. Chi requested copies in mock form of the draft labeling submitted to NDA 20-827. The "Questions" section on the Folding Carton and Educational Brochure has been updated to clarify the hours of operation for Advanced Care Products answer line.

We are sending eight desk copies directly to Dr. Chi and two copies to DDMAC. We respectfully request that this information be made part of NDA 20-827.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

Enclosed

Dr. Christina Chi

Advanced Care
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

January 13, 1998

Dr. Daniel Davis
Center for Drug Evaluation and Research (HFD-520)
Food and Drug Adminstration, Room S-342
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: **NDA 20-827**
MONISTAT 3 Vaginal Cream
Clinical Correspondence

Dear Dr. Davis:

As discussed in our conversation on 1/8/97, enclosed please find a desk copy of computer diskettes containing the exact Microsoft Word versions of Protocol 95-005-P, Protocol 95-007-P and the Overview of Two Controlled Clinical Studies from Item 11 p. 11-000006, Item 11 p. 11-001428 and Item 8 p. 08-000108, respectively, in our Original New Drug Application, NDA 20-827 MONISTAT® 3 (miconazole nitrate 4.0%) Vaginal Cream. Please note that the two protocol files are the same copies as the disks sent on 4/17/97.

We have not provided FDA with an Archive Copy, since this does not contain any new information. Please let me know if this meets your requirements.

These computerized versions of clinical information are being provided to facilitate your review of our NDA 20-827.

Should you have any questions or need additional information, please contact me directly at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron

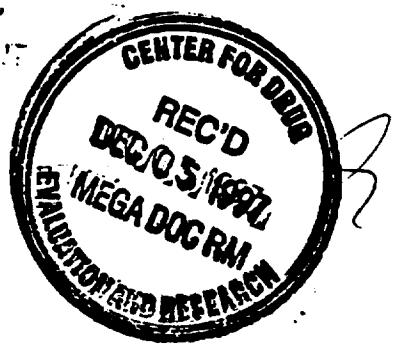
Diane Herron
Director, Regulatory Affairs

BC

ORIG AMENDMENT

DUPLICATE

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724



December 4, 1997

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

Amendment to Pending Application
Environmenal Assessment (EA)
NDA 20-827

MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Goldberger:

Reference is made to a question received from the agency on October 31, 1997 regarding the Environmental Assessment (EA) submitted as part of the subject New Drug Application (NDA). It was requested that the Expected Introduction Concentrations (EIC) be calculated based on total fifth year production estimates for all dosage forms and strengths included in the application or related applications. It further stated that this EIC (based on the entire product line) should be used to determine if the application qualifies for a Tier 0 EA. Reference is also made to the final rule regarding the National Environmental Policy Act published July 29, 1997 and more specifically to the categorical exclusions provided in 21 CFR §25.31 as a result of that final rule.

Advanced Care Products has calculated the EIC based on fifth year production estimates for the entire miconazole nitrate product line and has found that the application qualifies for a Tier 0 EA [redacted] A copy of the EIC calculation is attached to this letter, a revised EA is not being submitted as we are claiming a categorical exclusion from the EA requirement.

At this time, Advanced Care Products is claiming a categorical exclusion for the subject new drug application. Per §25.31(b), the subject NDA qualifies for a categorical exclusion as the action increases the use of the active moiety, but the estimated concentration at the point of entry into the aquatic environment will be less than 1 part per billion. Advanced Care Products has no knowledge of extraordinary circumstances that would affect this concentration calculation.

Should you have any questions regarding this amendment or the claimed categorical exclusion, please contact me directly at (732) 524-1675.

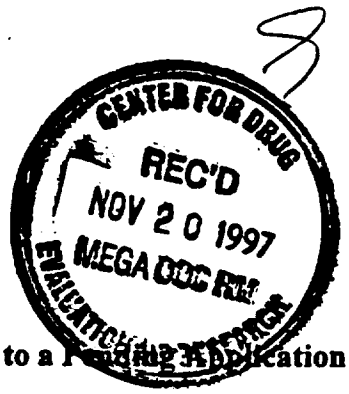
Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

NC
NEW CORRESP
DUPLICATE



November 19, 1997

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to a Pending Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Enclosed please find a copy of a Letter of Authorization that was inadvertently omitted from the Amendment to Pending New Drug Application, NDA 20-827 MONISTAT 3 Vaginal Cream submitted November 18, 1997. The Letter of Authorization from R.W. Johnson Pharmaceutical Research Institute authorizes Advanced Care Products to reference information from NDA 19-579 for TERAZOL® 7 Vaginal Cream and NDA 19-964 for TERAZOL® 3 Vaginal Cream.

We request that this letter be made part of the Amendment submitted November 18, 1997 and be included in the Archival Copy and the three reviewer's copies: Chemistry, Pharmacology and Clinical Data.

Should you have any questions, please feel free to contact me at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron for

Diane Herron
Director, Regulatory Affairs

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

OCT 24 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Review IV, HFD-590
Attn: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 19-964
TERAZOL® 3 (terconazole)
Vaginal Cream 0.8%

NDA 19-579
TERAZOL® 7 (terconazole)
Vaginal Cream 0.4%

Cross Reference Authorization

Dear Sir/Madam:

Reference is made to our approved New Drug Applications 19-964 for TERAZOL® 3 (terconazole) Vaginal Cream 0.8% and 19-579 for TERAZOL® 7 (terconazole) Vaginal Cream 0.4%. The R.W. Johnson Pharmaceutical Research Institute hereby authorizes the Food and Drug Administration to incorporate, by reference, said New Drug Applications in connection with a pending original New Drug Application 20-827 for MONISTAT® 3 (miconazole) 4% Vaginal Cream on behalf of the following:

Advanced Care Products, Personal Products Co.
A Division of McNeil - PPC
199 Grandview Road
Skillman, New Jersey 08558

Pleased by advised that the information contained within NDAs 19-964 and 19-579 are judged to be privileged and confidential trade secret data within the meaning of 5 USC section 552(b)(4) and 21 CFR section 20.61.

Should you have any questions and/or additional comments, please contact me directly at (908) 704-4879 or call our dedicated phone line for FDA use at (908) 704-4600.

Very truly yours,

Wayne Napoliello

Wayne Napoliello
Manager
Regulatory Affairs

Advanced Care
Route 1 South and Milltown Road. P.O. Box 6024
North Brunswick, New Jersey 08902-0724

November 18, 1997

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPHDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to a Pending Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversations that occurred on September 26 and October 1, 1997 between Dr. Christina Chi and Dr. Daniel Davis, Food and Drug Administration and Diane Herron, Advanced Care Products. The conversations focused on the safety of the base cream used in MONISTAT 3 Vaginal Cream and the length of time it has been marketed within the United States. Ms. Herron informed Drs. Chi and Davis that the base cream formulation was approved on March 21, 1997 for S-043 NDA 17-450 MONISTAT 7 Vaginal Cream and for the External Vulvar Cream used in NDA 20-288 MONISTAT 7 Combination Pack (S-001) and NDA 20-670 MONISTAT 3 Combination Pack (S-001). In addition it was discussed that the base cream formulation is very similar to the base formulation found in [redacted] and TERAZOL 3 Vaginal Cream (NDA 19-964). Subsequently, on October 6, 1997, Dr. Chi requested that we document the differences between the formulations of MONISTAT 3 Vaginal Cream and TERAZOL Vaginal Cream and provide information about the safety of the base formulation found in MONISTAT 3 Vaginal Cream.

We have addressed the above concerns in three reports, each discussing the differences between MONISTAT 3 Vaginal Cream and TERAZOL Vaginal Cream with different focus. The first report compares the MONISTAT 3 Vaginal Cream and TERAZOL 3 Vaginal Cream formulations and also provides the chemical basis for the differences in the base cream formulations. The second report provides a preclinical discussion of the excipients found in MONISTAT 3 Vaginal Cream and the safety of the levels at which the excipients occur in the base cream formulation. The third report provides a clinical discussion of the safety profile for the base cream formulation based on irritation, ADME and controlled clinical studies where TERAZOL formulations and placebo were evaluated as well as a review of the postmarketing experience for TERAZOL Vaginal Cream.

Amendment to a Pending Application
NDA 20-827
MONISTAT® 3 Vaginal Cream
November 18, 1997

As discussed in this submission, there are no additional safety concerns as a result of the differences in the formulations of MONISTAT 3 Vaginal Cream and Terazol 3 Vaginal Cream. The information presented about the safety of the excipients and the base cream formulation for MONISTAT 3 Vaginal Cream also shows that this formulation poses no additional safety concerns with respect over-the-counter treatment of vaginal candidiasis as presented in our unapproved New Drug Application for MONISTAT 3 Vaginal Cream, NDA 20-827.

We respectfully request that this information be made part of NDA 20-827 and we trust that you will find this submission satisfactorily addresses the issues as communicated to us by Dr. Christina Chi. Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

November 17, 1997

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

General Correspondence
Label Comprehension Study
NDA 20-827

MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Goldberger:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT® 3 Vaginal Cream, submitted March 31, 1997. Reference is made to our submission of a draft label comprehension study protocol on July 17, 1997 and to the agency's subsequent comments received via facsimile on September 8 and 9, 1997. At this time, Advanced Care Products is submitting a revised draft protocol including an analysis plan and a "drug facts" style label as well as a detailed response to the agency's comments.

We are providing this information in advance of a teleconference we have scheduled to discuss this protocol. The teleconference is scheduled for January 16, 1998 at 3:30 PM with your division as well as with the Over the Counter Drugs Division and Division of Drug Marketing, Advertising and Communications.

Should you have any questions, please contact me directly at (732) 524-1675.

Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

cc: Christina Chi, Ph.D.
Project Manager, Division of Special Pathogens and Immunologic Drug Products

Advanced Care
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

November 12, 1997

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversation that occurred on May 22, 1997 between Dr. Christina Chi, Food and Drug Administration and Diane Herron, Advanced Care Products. In this conversation, Dr. Chi communicated that the medical reviewers, Drs. Davis and Winfield, needed more information about the foreign data submitted in NDA 20-827 because it represents approximately 10% of the overall data submitted in the pivotal studies.

Enclosed please find a Foreign Data Summary in which we have discussed the applicability of the results from Latin American patients to the United States population with respect to baseline health, vaginal flora, standard of medical care and therapeutic cure rates. As discussed in this summary, no differences were observed in the foreign data that would adversely affect the applicability of the results to the United States population as presented in our unapproved New Drug Application for MONISTAT 3 Vaginal Cream.

We respectfully request that this information be made part of NDA 20-827 and we trust that you will find this submission satisfactorily answers the questions as communicated to us by Dr. Christina Chi.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron

Diane Herron
Director, Regulatory Affairs

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

October 8, 1997

Dr. Christina Chi
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

General Correspondence

NDA 20-827
MONISTAT 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Chi:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT 3 Vaginal Cream submitted March 31, 1997. Reference is also made to a proposed label comprehension study protocol submitted on July 17, 1997 and to the subsequent comments received from the reviewing divisions on September 8-9, 1997. Reference is also made to the teleconference that had been scheduled for October 31, 1997 at 9:15am to discuss these specific recommendations made by the reviewers.

As we discussed in a telephone conversation on October 7, 1997, Advanced Care Products (ACP) has requested the cancellation of the above-mentioned teleconference. We require additional time to prepare a second draft protocol as well as to prepare a second set of labels incorporating elements of the proposed standardized OTC label and simplified language to use as a comparator in the proposed study.

At this time, we wish to thank you, Dr. Chi, for re-scheduling this meeting, which will be a teleconference, for December 1, 1997 at 1:15pm. We understand it will be for one hour. We will be sending our proposed label comprehension study protocol for review prior to this date. We will also provide a list of attendees for ACP at that time.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron

Diane Herron
Director, Regulatory Affairs

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

October 7, 1997

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream which was submitted on March 31, 1997. Reference is also made to two sets of questions from the microbiological reviewer, as communicated to us by Dr. Christina Chi on 5/22/97 and 6/2/97.

Enclosed please find the responses to the two sets of questions previously submitted as desk copies, per Dr. Chi's instructions. The response to the first set of questions was previously communicated by fax on 5/28/97 and the response to the second set of questions was submitted by hard copy on 6/3/97.

At Dr. Chi's request on 10/7/97, we would like to submit this information for inclusion in our NDA 20-827 file. This amendment is being provided in one Archival Copy (blue binder).

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron

Diane Herron
Director, Regulatory Affairs

- Also will be sent in to the doc room on 3/29/98

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

September 23, 1997

Christina Chi, Ph.D.
Project Manager
Food and Drug Administration
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
9201 Corporate Boulevard
Rockville, MD 20850

General Correspondence

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Chi:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT® 3 Vaginal Cream, submitted March 31, 1997. Reference is also made to a proposed label comprehension study protocol submitted on July 17, 1997 in response to a request from the agency and to the subsequent comments received from the reviewing divisions on September 8-9, 1997.

Advanced Care Products is requesting that the proposed label comprehension study be considered a post-approval requirement for the subject NDA. We believe, after reviewing the comments received, the objective is not only to study the effectiveness of the label for the product under review, but to study the class labeling and evaluate it for the broader purpose of revising class labeling. Requiring such an extensive study as a condition of approval for what is simply a new dosage form of an existing 3-day therapy seems excessive, especially since it would be the only product in the class required to conduct such a study prior to approval. We firmly believe the study outlined in the comments received will provide valuable information to aid in the development of more effective class labeling and do not object to sponsoring such a study, however we believe it should be considered a post-approval commitment for the pending NDA.

We look forward to scheduling a face-to-face meeting with the reviewing divisions to further discuss our position and the comments received. Please contact me at (732) 524-1675 if you have any questions.

Very truly yours,
ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

8

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

August 12, 1997

David Feigal, Jr., M.D.
Acting Director
Food and Drug Administration
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-827
Amendment to Pending Application
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Feigal:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT® 3 Vaginal Cream, submitted March 31, 1997. Reference is made to your FAX dated July 29, 1997, wherein it was requested that we provide additional PK parameter determinations. Specifically, the AUC (0-24) for the final doses of study drugs, for individual subjects and by treatment group (mean, ± sd, range), was requested. Individual miconazole plasma concentration and PK parameters were also requested in electronic format.

At this time we are providing the requested datasets and diskettes for pharmacokinetics study 95-009-P. This information is being paginated as a continuation of NDA Item 6, Human Pharmacokinetics and Bioavailability and is being provided in one desk copy and one archival copy. The desk copy is bound in orange for the Pharmacokinetics Reviewer (Item 6) while the Archival Copy is bound in blue.

Should you have any questions or need additional information, please contact me directly at (908) 524-1675.

Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

cc: Christina Chi, Ph.D.
Project Manager, Division of Anti-Infective Drug Products

Enclosures: Volume 2.1 (Archival, Pharmacokinetic)

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

July 17, 1997

Debra Bowen, M.D.
Director
Food and Drug Administration
Division of OTC Drug Products (HFD-560)
9201 Corporate Boulevard
Rockville, MD 20850

General Correspondence

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Bowen:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT® 3 Vaginal Cream, submitted March 31, 1997. Reference is made to a phone contact of May 30, 1997 between Diane Herron (Advanced Care Products) and Christina Chi (Anti-Infective Division) when a label comprehension study was suggested for the subject product. Reference is also made to phone contacts of June 23 and 25, 1997 between Diane Herron (Advanced Care Products) and Sakineh Walker (OTC Division) to further discuss submission of the draft protocol for the division's review.

As requested, we are supplying a draft protocol for a label comprehension study to evaluate the overall comprehension of the proposed label for MONISTAT® 3. To assist your review, we are also supplying a mock-up of the label we are proposing to use in this study. Please note that this proposed label contains the same format and label information used for our MONISTAT® products as well as all other OTC vaginal yeast infection products.

As stated in the protocol, the study will include 400 women and will be conducted in 20 geographically dispersed malls. Prior yeast infection(s) will not be an inclusion requirement as we wish to evaluate if the label provides appropriate information for all women ages 18-49 to adequately self-select for this type of product.

In a prior conversation with the division (June 25) it was indicated that it would take approximately 1-2 weeks to review the draft protocol. We are therefore requesting a conference call to discuss the study with the division as soon as this review is complete. Please note that we

are planning to field this study in early August and look forward to the division's comments so that the best protocol can be developed.

Should you have any questions, please contact me directly at (908) 524-1675. 1316

Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

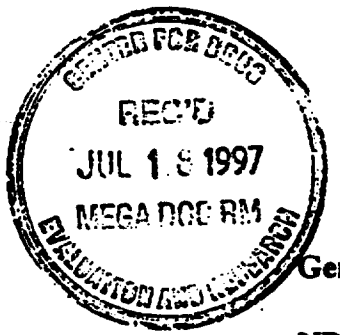
cc: Christina Chi, Ph.D.
Project Manager, Division of Anti-Infective Drug Products

APPEARS THIS WAY
ON ORIGINAL

Extra

DUPLICATE

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724



July 17, 1997

Debra Bowen, M.D.
Director
Food and Drug Administration
Division of OTC Drug Products (HFD-560)
9201 Corporate Boulevard
Rockville, MD 20850

General Correspondence

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)

Dear Dr. Bowen:

Please refer to the pending New Drug Application (NDA) 20-827 for MONISTAT® 3 Vaginal Cream, submitted March 31, 1997. Reference is made to a phone contact of May 30, 1997 between Diane Herron (Advanced Care Products) and Christina Chi (Anti-Infective Division) when a label comprehension study was suggested for the subject product. Reference is also made to phone contacts of June 23 and 25, 1997 between Diane Herron (Advanced Care Products) and Sakineh Walker (OTC Division) to further discuss submission of the draft protocol for the division's review.

As requested, we are supplying a draft protocol for a label comprehension study to evaluate the overall comprehension of the proposed label for MONISTAT® 3. To assist your review, we are also supplying a mock-up of the label we are proposing to use in this study. Please note that this proposed label contains the same format and label information used for our MONISTAT® products as well as all other OTC vaginal yeast infection products.

As stated in the protocol, the study will include 400 women and will be conducted in 20 geographically dispersed malls. Prior yeast infection(s) will not be an inclusion requirement as we wish to evaluate if the label provides appropriate information for all women ages 18-49 to adequately self-select for this type of product.

In a prior conversation with the division (June 25) it was indicated that it would take approximately 1-2 weeks to review the draft protocol. We are therefore requesting a conference call to discuss the study with the division as soon as this review is complete. Please note that we

are planning to field this study in early August and look forward to the division's comments so that the best protocol can be developed.

Should you have any questions, please contact me directly at (908) 524-1675. 1316

Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

cc: Christina Chi, Ph.D.
Project Manager, Division of Anti-Infective Drug Products

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

Not new info

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

8

7/2/97. stamp date 7/3/97
orig. (doc type) , N
minor statistical.
(see the cover letter)

July 2, 1997

Carmen DeBelles
Food and Drug Administration
Division of Special Pathogens ar
Immunologic Drug Products (HF-
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Subject: **NDA 20-827**
Correspondence

35

NDA ORIG AMENDMENT

Dear Mr. DeBelles,

Reference is made to our Original New Drug Application, NDA 20-827 for MONISTAT® 3 Vaginal Cream, which was dated March 31, 1997. Reference is also made to your FAX dated June 26, 1997, wherein it was requested that we provide SAS datasets for the Statistical Reviewer and Access datasets for the Medical Reviewer of specified data, for assisting in the review of our application. At this time we are sending the datasets for safety and efficacy studies #95-005 and #95-007 submitted on diskettes with corresponding documentation. This information has been paginated as a continuation of NDA Item 8, Clinical Section and Item 10, Statistical Section. We respectfully request that this correspondence be added to our NDA 20-827.

The subject information is being provided in two desk copies: one consists of the datasets for the Medical Reviewer (Item 8), bound in light brown and the other consists of the datasets for the Statistical Reviewer (Item 10), bound in green. Please note that we have not numbered these volumes on the covers. Since this correspondence does not contain any new information, the Archive Copy consists of this letter only.

Should you have any questions or need additional information, please contact me directly at 908-524-1675.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Very Truly Yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

cc: Mr. Carmen DeBelles (w/o attachments) via fax

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

June 3, 1997

Dr. Christina Chi
Center for Drug Evaluation and Research (HFD-520)
Food and Drug Administration, S357
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Chi:

Enclosed herewith are the answers to the second set of questions from the Microbiology Reviewer regarding NDA 20-827 sent on 6/2/97. An article describing the different species of yeasts that can grow on BiGGY agar and a complete listing of all yeasts that grew from Protocols 95-005-P and 95-007-P are also attached for review.

If you need additional information, please contact me directly at 908-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Rhea N. Williams for

Diane Herron
Director, Regulatory Affairs

FILED THIS WAY
ON ORIGINAL

Answers to Microbiology Questions

Attachment I
Nickerson (1953) Article

Attachment II

Specimen Report: 95-007-P

ORIGINAL

8

Advanced Care Products
691 Highway 1, P.O. 6024
North Brunswick, New Jersey 08902-0724

87
NDA ORIG AMENDMENT

May 9, 1997

Dr. Feigal, Jr., M.D.
Acting Director
Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
5600 Fishers Lane
Rockville, MD 20857

Amendment to Unapproved
Original New Drug Application

NDA 20-827
MONISTAT 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Feigal,

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream which was submitted on March 31, 1997. Reference is also made to a request from the statistical review team, as communicated to us by Dr. Christina Chi on April 21, 1997, for subgroup analysis of the primary efficacy variable.

Therefore, we are submitting herewith an Addendum to the two clinical safety study reports, #95-005 and 95-007 which presents results of our additional analysis. In a conversation between ACP representatives and Nancy Silliman on May 5, 1997, to clarify the specific subgroups required, she confirmed that age and race were appropriate and these results would fulfill their request for additional information. We respectively request that you include this information in our NDA 20-827 file.

This amendment is being provided in three copies, the Archival Copy (blue binders) and two review copies: Clinical (tan binders) and Statistical (green binders). In addition, Desk Copies are being sent under separate cover directly to Nancy Silliman (Room S-308) and Dr. Daniel Davis (Room S-342). Dr. Davis' copy also includes the information on computer diskette.

Should you have any further questions or need additional information, please contact me directly at (908) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron

Diane Herron
Director, Regulatory Affairs

Extra
8

Advanced Care Products
691 Highway 1, P.O. 6024
North Brunswick, New Jersey 08902-0724

Received
5/13/97
C Davis

Addendum #1

May 9, 1997

Dr. Feigal, Jr., M.D.
Acting Director
Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
5600 Fishers Lane
Rockville, MD 20857

Amendment to Unapproved
Original New Drug Application

NDA 20-827
MONISTAT 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Feigal,

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream which was submitted on March 31, 1997. Reference is also made to a request from the statistical review team, as communicated to us by Dr. Christina Chi on April 21, 1997, for subgroup analysis of the primary efficacy variable.

Therefore, we are submitting herewith an Addendum to the two clinical safety study reports, #95-005 and 95-007 which presents results of our additional analysis. In a conversation between ACP representatives and Nancy Silliman on May 5, 1997, to clarify the specific subgroups required, she confirmed that age and race were appropriate and these results would fulfill their request for additional information. We respectively request that you include this information in our NDA 20-827 file.

This amendment is being provided in three copies, the Archival Copy (blue binders) and two review copies: Clinical (tan binders) and Statistical (green binders). In addition, Desk Copies are being sent under separate cover directly to Nancy Silliman (Room S-308) and Dr. Daniel Davis (Room S-342). Dr. Davis' copy also includes the information on computer diskette.

Should you have any further questions or need additional information, please contact me directly at (908) 524-1675.

Sincerely,

Advanced Care Products

Diane Herron

Diane Herron
Director, Regulatory Affairs

X

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

April 7, 1997

Ms. Sakineh Walther
Consumer Safety Officer
Division of OTC Drugs, Room S240
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Ms. Walther:

As per our conversation on April 4, 1997, enclosed please find the additional desk copies of Volume 1.1 (Item 1: Overall NDA Index, Item 2: Application Summary and Item 4c: Labeling) and Volumes 1.8, 1.9 and 1.10 (Item 8: Clinical Data) from our Original New Drug Application, NDA 20-827 MONISTAT® 3 (miconazole nitrate 4.0%) Vaginal Cream. Should you have any questions or need additional information, please contact me directly at 908-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director
Regulatory Affairs

APPEARS THIS WAY
ORIGINAL

fax dated: 5/23/97 : Response of micro questions from L Fosey

ORIGINAL

2

Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

BS

NDA ORIG AMENDMENT

4/3/97 stamp 4/9/97
Orig doc-type
= N.
minor statistical

April 3, 1997

Dr. David Feigal, Jr., M.D.
Acting Director
Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Feigal,

(get the cover ltr)

Reference is made to our Original New Drug Application, NDA 20-827 for MONISTAT® 3 Vaginal Cream which is dated March 31, 1997. Reference is also made to telephone conversations between ourselves at ACP and Dr. Daphne Lin between 3/11/97 and 3/31/97 regarding the submission of data on computer diskettes for assisting in the statistical review of our application. At this time we are sending the datasets for safety and efficacy studies #95-005 and #95-007 submitted on diskettes with corresponding documentation. This information has been paginated as a continuation of NDA Item 10, Statistical Section, beginning with page # 10-000234. We have also included a Table of Contents. This completes the statistical section of our pending application. We respectfully request that this information be added to our NDA 20-827.

The subject information consists of one volume, which we have labeled as, "DESK COPY". We have provided 2 copies, an FDA Archival copy, bound in blue FDA binders, and a Review copy, bound in green. Please note that we have not numbered these volumes on the covers.

Should you have any questions, please call me directly at (908) 524-1675.

Very Truly Yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG
REC'D
APR 04 1997

ORIGINAL 8
Receipt date.
March 31, 1997

Advanced Care Products
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

March 31, 1997

Dr. David Feigal, Jr., M.D.
Acting Director
Food and Drug Administration
Division of Anti-Infective Drug Products (HFD-520)
5600 Fishers Lane
Rockville, MD 20857

Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. # 3216

Dear Dr. Feigal,

In accordance with the provisions of Section 505(b) of the Federal Food, Drug and Cosmetic Act and Title 21 of the Code of Federal Regulations, 21 CFR§314.50, we submit herewith a New Drug Application for Miconazole Nitrate 4.0% Vaginal Cream. This application has been preassigned NDA #20-827.

We propose to market this product over-the-counter under the tradename MONISTAT® 3 Vaginal Cream. It is indicated as a 3-day treatment of vaginal yeast infections (candidiasis) and labeled to be used by women who have been previously diagnosed by a doctor and recognize the same condition again.

Miconazole nitrate 4.0% vaginal cream has been evaluated clinically under our [redacted]
Miconazole nitrate has been extensively studied in various dosage forms under various INDs in the United States and also by our foreign affiliates. This active ingredient is the subject of six approved New Drug Applications specifically for vaginal candidiasis, as follows:

NDA 17-450 MONISTAT® 7 (100mg) Vaginal Cream
approved as 14-day Rx 1/30/74
approved as 7-day Rx 7/28/77
approved OTC 2/15/91
NDA 18-520 MONISTAT® 7 (100mg) Vaginal Suppositories
approved Rx 3/15/82
approved OTC 2/15/91
NDA 18-888 MONISTAT® 3 (200mg) Vaginal Suppositories
approved Rx 8/15/84
NDA 18-592 MONISTAT® 5 (100mg) Tampon
approved Rx 10/27/89
NDA 20-288 MONISTAT® 7 Combination Pack 22
(100mg suppositories and External Vulvar Cream)
approved OTC 4/26/93
NDA 20-670 MONISTAT® 3 Combination Pack 22
(200mg suppositories and External Vulvar Cream)
approved OTC 4/16/96

Currently, miconazole nitrate formulations for vaginal use are sold in 94 countries outside of the United States, and are available without a prescription in 34 of those countries.

This application presents the results of two active controlled clinical studies demonstrating that miconazole nitrate 4.0% vaginal cream, administered in a 200mg dose once a day for 3 days is therapeutically equivalent to the OTC treatment, MONISTAT® 7 Vaginal Cream given 100mg per day for 7 days. It also has been shown to have an adverse experience profile similar to currently marketed MONISTAT® 7 Vaginal Cream in all of the studies in this NDA.

The dosage is identical to the currently marketed MONISTAT® 3 Combination Pack with 200mg suppositories given for 3 days. Thus, miconazole nitrate 3-day vaginal cream provides the benefit of the shorter therapy regimen in the consumer preferred cream form, with no increase in risk to the patient.

This drug product will be manufactured, labeled and tested at Ortho Pharmaceuticals, a Division of OMJ Pharmaceuticals, Inc. Manati, Puerto Rico. A field copy of the two volumes of this submission which contains Chemistry, Manufacturing and Control information (Item 3), the application form (Form FDA 356h), and the application summary (Item 2) is being forwarded directly to the FDA San Juan Office. We certify that the field copy is a true copy of the information contained in the archival and review copies of this New Drug Application.

Please refer to the Overall Reviewer's Guide located in this volume (Vol. 1.1) of this NDA for information regarding the organization of this application.

Additionally, [redacted] was sent under separate cover to the FDA [redacted].

Should you have any questions, please contact me directly at (908) 524-1675.

Very truly yours,

Diane Herron

Diane Herron
Director, Regulatory Affairs
Advanced Care Products

590 Chi

NOV 3 1997

NDA 20-827

MEMORANDUM OF TELECON

DATE: October 1, 1997

APPLICATION NUMBER: NDA 20-827 Monistat 3 Cream, miconazole 4%

BETWEEN SPONSOR:

Advance Care Products:
Diane Herron, Director, Regulatory Affairs
Lynn Pawelski, Manager, Regulatory Affairs
Rhea Williams, Regulatory Affairs

AND FDA:

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

Division of Over the Counter Drug Products, HFD-560:
Ling Chin, M.D., Medical Officer
Cheryl Turner, R.N., Interdisciplinary Scientist
Sakineh Walther, Project Manager

Division of Special Pathogen and Immunologics Drug Products, HFD-590:
Christina Chi, Ph.D., Project Manager
Daniel Davis, M.D., Medical Officer

SUBJECT: FDA response to sponsor's request to conduct the labeling comprehension study as a phase IV commitment.

DISCUSSION POINTS:

* Dr. Chin referred to the sponsor's September 23, 1997 fax and strongly encouraged them to conduct a label comprehension study. She indicated that the sponsor would benefit from the information obtained from this study.
* Dr. Chin stated that the FDA would prefer that the sponsor conduct the study now, but that it would be acceptable to conduct the study during phase IV.
* Dr. Chin mentioned that the FDA has safety concerns regarding the new base formulation for the 4% cream since it has no marketing history. The sponsor confirmed that the product has not been previously marketed in the new formulation but that safety information could be extrapolated from previously marketed formulations, such as the Monistat suppository,

miconazole 200 mg, and the Terazole cream, miconazole 0.4% and 0.8%; the latter having very similar excipients.

* Dr. Davis indicated that Terazole's safety data would be helpful. The sponsor responded that they would provide it in summary form as soon as possible, and in detail upon further request.
* The sponsor expressed that their marketing people would like to talk with the FDA regarding the planning of the labeling comprehension study, especially the study design.
* To increase efficiency, the FDA conveyed to the sponsor that they should provide their comments and questions concerning the label comprehension study in writing prior to the next telecon or meeting.
* The sponsor responded that this might not be done prior to October 8, 1997.

The telecon was adjourned amicably.

/S/
Christina Chi, Ph.D.
Nov. 1, 1997

Concurrence only: HFD-590/MO/DDavis
11/1/97

cc: Original NDA 20-827
HFD-40/SSA/KLechter10/8/97
HFD-560/MO/LChin10/30/97
HFD-560/PM/SWalther
HFD-560/IS/CTurner
HFD-590/Div.File
HFD-590/ClinTL/BLeissa
HFD-590/ClinRev/DDavis10/2/97
HFD-590/SPM/PFogarty
HFD-590/PM/Christina Chi

Drafted and prepared by: CTurner & CChi 10/2/97

TELECON, Advance Care Products.

Date: 7/14/97

From: Christina Chi, 301-827-2155

Subject: NDA: 20-827 Monistat-3 Vaginal Cream Review Progress Meeting 1
(Due date: March 30, 1998)

To: Ling Chin, Philip Colangelo, Daniel Davis, Cheryl Dixon, Linda Gosey, Dorota Matecka, Owen McMaster, JoAnn Spearmon, Mathew Thomas, Sakineh Walther.

Attendees: Colangelo, Davis, Dixon, Gosey, Matecka, Spearmon, Walther, Chi.

Discussion:

Chemistry: EER requested and is pending. No anticipated problem with the formulation since it is similar to Monistat-7. Will look at method validation and specification.

Pharmacology:(Message sent through EM:)No issue.

BioPharmaceutics: Review in the queue; will start after Dec. and could be done in a month.

Microbiology:Questions to ACP replied. Review is in the queue; no real issues to be concerned about.

Clinical: Will analyze a random sampling of patients (provided by the statisticians) and compare the efficacy results in this group with the entire patient population in the clinical trial. Predicted efficacy from the worst case scenario: +/- 60%. Will be done max. early Jan. '98.

Statistics: A few questions to ACP such as coding aren't replied yet.

DDMAC: No issues.

OTC: Ling is on vacation. Sakineh reported that no apparent issues are anticipated in the safety review.

Next review progress meeting: early October and December 1997.
Estimated labeling meeting: early February 1997.

there is no need for DSI investig (see DSI section)

Dan Davis' X

Date: 7/14/97

From: Christina Chi, 301-827-2155

Subject: NDA: 20-827 Monistat-3 Vaginal Cream Review Progress Meeting 1
(Due date: March 30, 1998)

To: Ling Chin, Philip Colangelo, Daniel Davis, Cheryl Dixon, Linda Gosey, Dorota Matecka, Owen McMaster, JoAnn Spearmon, Mathew Thomas, Sakineh Walther.

Discussion:
Pharmacology: (Message sent through EM:) No issue.

BioPharmaceutics: Review in the queue; will start after Dec. and could be done in a month.

Microbiology: Questions to ACP replied. Review is in the queue; no real issues to be concerned about.

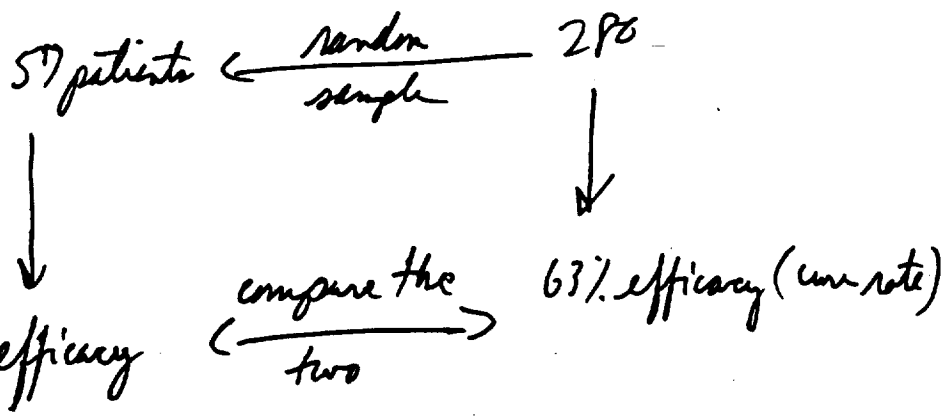
Clinical: ~~Start doing~~ Analyze a random sampling of patients (provided by the statistatitians) ~~to see how close the evaluation is.~~ + compare the efficacy results in this group with the entire pt population in the clinical trial
Predicted efficacy from the worst case scenario: +/- 60%. Will be done max. early Jan. '98.

Statistics: A few questions to ACP such as coding aren't replied yet.

DDMAC: No issues.

OTC: Ling is on vacation. Sakineh reported that no apparent issues are anticipated in the safety review.

Next review progress meeting: early October and December 1997.
Estimated labeling meeting: early February 1997.



Advanced Care Products
Route 1 South and Milltown Road, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

June 3, 1997

Dr. Christina Chi
Center for Drug Evaluation and Research (HFD-520)
Food and Drug Administration, S357
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Chi:

Enclosed herewith are the answers to the second set of questions from the Microbiology Reviewer regarding NDA 20-827 sent on 6/2/97. An article describing the different species of yeasts that can grow on BiGGY agar and a complete listing of all yeasts that grew from Protocols 95-005-P and 95-007-P are also attached for review.

If you need additional information, please contact me directly at 908-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Rhea N. Williams for

Diane Herron
Director, Regulatory Affairs

1 separate disk copy (+thick) only to C. Chi
Made 1 copy for L.S 6/5/97
2 1 more on 10/6/97

NDA ACKNOWLEDGEMENT LETTER

NDA 20-827

Attention: Diane Herron, Director, Regulatory Affairs
P.O. Box 6024,
691 U.S. Route 1 South
North Brunswick, New Jersey 08902

Dear Ms. Herron :

We have received your new drug application (NDA) submitted under section 505(b)/507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Monistat 3 (miconazole nitrate) Vaginal Cream
4%

Therapeutic Classification: _____

Date of Application: March 31, 1997

Date of Receipt: March 31, 1997

Our Reference Number: NDA 20-827

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)/507 of the Act on in accordance with 21 CFR 314.101(a).

Should you have any questions, please call: /S/
Project Manager
(301) 827-2125

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

Sincerely yours,

James D.Bona ,R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Goldberger

Advanced Care Products
Personal Products Company, Division of McNeil-PPC, Inc.
691 Highway 1, P.O. Box 6024
North Brunswick, New Jersey 08902-0724

January 29, 1998

Dr. Mark Goldberger
Food and Drug Administration
Center for Drug Evaluation and Research
DSPIDP (HFD-590)
9201 Corporate Boulevard
Rockville, Maryland 20850

Amendment to Pending
Original New Drug Application

NDA 20-827
MONISTAT® 3 Vaginal Cream
(miconazole nitrate 4.0%)
User Fee I.D. #3216

Dear Dr. Goldberger:

Reference is made to our unapproved New Drug Application, NDA 20-827 for MONISTAT 3 Vaginal Cream, which was submitted on March 31, 1997. Reference is also made to the conversation that occurred on January 23, 1998 between Dr. Christina Chi, Food and Drug Administration and Rhea Williams, Advanced Care Products. In this conversation, Dr. Chi requested copies in mock form of the draft labeling submitted to NDA 20-827. The "Questions" section on the Folding Carton and Educational Brochure has been updated to clarify the hours of operation for Advanced Care Products answer line.

We are sending eight desk copies directly to Dr. Chi and two copies to DDMAC. We respectfully request that this information be made part of NDA 20-827.

Should you have any further questions or need additional information, please contact me directly at (732) 524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron

Diane Herron
Director, Regulatory Affairs

Enclosed