



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

May 4, 1999

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

PENDING NDA 20-968
Miconazole Nitrate 1200 mg Vaginal [redacted] and 2% External Cream

Dear Dr. Goldberger:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream (proposed name "MONISTAT 1 Dual Pak") for treating vaginal candidiasis. Reference is also made to a November 5, 1998 fax from the CDER Labeling and Nomenclature Committee regarding the proposed proprietary name and to our March 1, 1999 submission of potential new names for the OTC one-dose tioconazole product we currently market as MONISTAT 1.

Advanced Care Products (ACP) is proposing two new names for consideration as a new name for the tioconazole product we market. ACP will change the tioconazole product's name to either TC MONISTAT or TL MONISTAT (based on which name the agency finds preferable) as of September 1, 1999. This will be planned to coincide with the launch of the pending NDA product, MONISTAT 1 Dual-Pak (Miconazole Nitrate 1200 mg Vaginal [redacted] and 2% External Cream). At this time we would also like to request a meeting with the agency as soon as possible to discuss these proposed names and associated implementation strategies in order to come to an efficient resolution of this naming issue.

ACP has conducted some additional research to investigate new product names that would impart a difference to the consumer versus our base brand, miconazole nitrate, MONISTAT products. We are submitting the results of this research for your consideration at this time. These names do contain the MONISTAT base, but include a prefix (TC or TL) before the base name MONISTAT. The research conducted has shown that the prefixes have a greater degree of difference from MONISTAT 1 than do suffixes. The research has also shown that the prefixed names being proposed (TC MONISTAT, TL MONISTAT) are very close to being as different from MONISTAT 1 as the previously approved VAGISTAT 1[®] is. We would like the agency to consider this new data before coming to a decision on this naming issue.

ACP would like to restate that we agree with the agency that discerning a difference between the tioconazole product and miconazole nitrate products is desirable for consumer information and education. We believe that the proposed nomenclature, including the use of alpha rather than numeric designations as well as the use of prefixes instead of suffixes, is quite different for this class of products in which all products are suffixed with a numeric duration of therapy. The proposed name for the tioconazole product would make this product the only one with a prefix and the only one without a numeric suffix, a huge point of differentiation from both the competition and other MONISTAT (miconazole nitrate) products. It is also important to point out that this difference also brings this new name into a similar differentiation from MONISTAT 1 as VAGISTAT.

We feel that maintaining this product within the MONISTAT family is important from a consumer support standpoint. We (ACP) provide a wealth of consumer information and help through our 1-800 and website support. Consumers have found this useful and important and should continue to expect this support from MONISTAT.

We also feel that applying the current branding of the MONISTAT umbrella to the tioconazole product – as proposed – is not misleading. With both the MONISTAT miconazole nitrate and tioconazole products, consumers can expect (and in fact do receive) the same benefit (curing a yeast infection) with a similar side effect (risk) profile. In this respect, we believe that the proposed naming scenario is again, not misleading. We believe that the miconazole nitrate and tioconazole products offered under the same brand umbrella come with the same set of expectations and benefits and therefore cannot be considered misleading.

We ask that the agency choose either TC MONISTAT or TL MONISTAT and provide us with feedback at the meeting we have requested herein. We trust that this is a complete response to the issues raised and that we can set up a meeting as soon as possible to discuss these naming issues and reach a resolution. If you have any questions, please feel free to contact me at (732)-524-1675. We look forward to achieving a timely resolution to this issue.

Sincerely,



Diane Herron
Director, Regulatory Affairs

Attachments: Archive Copy (letter, overview, unbound Brand Institute Report)
Review Copies (letter, overview, bound Brand Institute Report)

cc: Christina Chi, Project Manager, DSPIDP (HFD-590) – Desk copy w/o attachments



Advanced Care Products

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

May 3, 1999

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

AMENDMENT TO PENDING APPLICATION
Pending NDA 20-968
Miconazole Nitrate Vaginal [redacted] and External Cream

Dear Dr. Goldberger:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream for treating vaginal candidiasis. Reference is also made to a facsimile, dated April 27, 1999. At this time, Advanced Care Products (ACP) is responding to the requests in the facsimile and request that this information be made part of our pending application.

One of the requested items, an electronic copy of the revised draft labeling, was submitted on April 27, 1999. The diskette included updated copies of the non-annotated physician package insert, trade folding carton, and patient package insert. Therefore, we are not including an additional copy in this submission.

On the enclosed diskette, there are tables of drug-related adverse events that compare the 1200 mg [redacted] to MONISTAT® 7. This includes all drug-related adverse events considered possibly, probably, or highly probably related to study drug that occurred in 1% or greater in either of the two treatment arms. These listings are broken-out into three tables. Table 1 lists all drug-related adverse events from study 96-002, Table 2 lists all drug-related adverse events from study 97-006, and Table 3 lists all the drug-related adverse events from both studies combined.

Please feel free to contact me directly at 732-524-1675 if you have any questions.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron
Diane Herron
Director, Regulatory Affairs

cc: Christina Chi, Project Manager, DSPIDP (HFD-590)

TABLE 1

**Drug Related Adverse Events by Body System
With an Incidence of Greater Than 1% in Either Treatment Group
Protocol: 96-002-P**

Body System/Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal (N = 264)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 233)	
	n	%	n	%
Gastrointestinal				
Cramps, GI	4	1.5	0	0.0
Nausea	3	1.1	0	0.0
Genital/Reproductive				
Burning, Female Genitalia	25	9.5	27	11.5
Discharge, Female Genitalia	7	2.7	0	0.0
Irritation, Female Genitalia	14	5.3	8	3.4
Pruritus, External Female Genitalia	17	6.4	23	9.8
Nervous System				
Headache	6	2.3	1	0.4

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 2

**Drug Related Adverse Events by Body System
With an Incidence of Greater Than 1% in Either Treatment Group
Protocol: 97-006-P**

Body System/Adverse Experience	Treatment Group			
	MCN (1200 mg) Vaginal (N = 254)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 231)	
	n	%	n	%
Genital/Reproductive				
Burning, Female Genitalia	25	9.8	26	11.3
Discharge, Female Genitalia	5	2.0	2	0.9
Edema, Female Genitalia	3	1.2	2	0.9
Erythema, Female Genitalia	3	1.2	3	1.3
Irritation, Female Genitalia	21	8.3	25	10.8
Pruritus, External Female Genitalia	16	6.3	23	10.0

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 3

**Drug Related Adverse Events by Body System
With an Incidence of Greater Than 1% in Either Treatment Group
Combined Protocols: 96-002-P and 97-006-P**

Body System/Adverse Experience	Treatment Group			
	(MCN) 1200mg Vaginal [redacted] (N = 518)		MONISTAT® 7 (2% MCN) Vaginal Cream (N = 464)	
	n	%	n	%
Gastrointestinal				
Cramps, GI	5	1.0	0	0.0
Nausea	3	0.6	0	0.0
Genital/Reproductive				
Burning, Female Genitalia	50	9.7	53	11.4
Discharge, Female Genitalia	12	2.3	2	0.4
Edema, Female Genitalia	3	0.6	3	0.6
Erythema, Female Genitalia	3	0.6	3	0.6
Irritation, Female Genitalia	35	6.8	33	7.1
Pruritis, External Female Genitalia	33	6.4	46	9.9
Nervous System				
Headache	7	1.4	1	0.2

**APPEARS THIS WAY
ON ORIGINAL**



Advanced Care Products

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

April 27, 1999

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4/27/99*

*151
med. AP-28*

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

GENERAL CORRESPONDENCE

Pending NDA 20-968

Miconazole Nitrate Vaginal [] and External Cream

Dear Christina Chi:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [] and 2% external cream for treating vaginal candidiasis. Reference is also made to our previous submission of April 19, 1999 in which Advanced Care Products included updated draft labeling. At this time, we are submitting electronic copies of that labeling, for ease of review. The diskette contents are as follows:

The documents contained on this diskette was created using Microsoft Word 97.

DISK CONTENTS:

Document Name	Disk File Name	File Size
Non-annotated Physician Package Insert	DRINSERT041999.DOC	82KB
Trade Folding Carton	FDLGCRTN041999.DOC	22KB
Patient Package Insert	PTINSERT041999.DOC	42KB

If you have any questions, please contact me directly at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron
Director, Regulatory Affairs

Cc: Dr. Christina Chi, Project Manager, DSPIDP (HFD-590)

MAR 29 1999

Division of Over-the-Counter Drug Products
Labeling Review

Pending NDA#: 20-968

DRUG PRODUCT: Miconazole Nitrate Vaginal [redacted] and External Cream

ACTIVE INGREDIENT: Miconazole Nitrate Vaginal [redacted] (1200 mg), plus external cream (miconazole nitrate cream (2%))

INDICATION: "For the treatment of vaginal yeast infections and the relief of itching and irritation on the skin outside the vagina (vulva) associated with a yeast infection."

SPONSOR: Advanced Care Products

TYPE OF SUBMISSION: Proposed OTC switch package containing an OTC actual use study (protocol 98-006-P) and draft labeling.

DATE OF SUBMISSION: January 12, 1999

DATE OF REVIEW: March 15, 1999

REVIEWER: Cheryl Turner, IDS

PROJECT MANAGER: Elizabeth Yuan

BACKGROUND:

Advanced Care Products submitted this OTC switch package for miconazole nitrate for treatment of vulvovaginal candidiasis on January 12, 1999. The firm is requesting feedback on a protocol for an OTC actual use study entitled: "A Single-Blind Observational Study to Evaluate the Safety Profile of a 1200 mg Miconazole Nitrate Vaginal [redacted] Combination Pack in the Treatment of Vaginal Yeast Infection." This review is of the draft labeling (folding carton and educational brochure) submitted for this pending NDA.

Our comments and revisions for the carton and educational brochure are in Attachment 1. Areas to be deleted are identified by a single strike out line. The Agency's recommended revisions are double-underlined.

Reviewer's Comments and Recommendations:

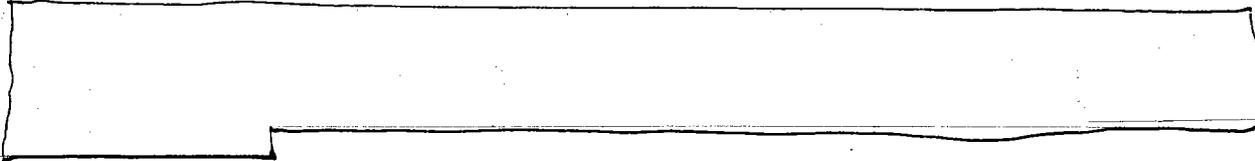
1. Product Name:

The name "One Dose Vaginal Yeast Infection Treatment" may be misleading. Although this combination product contains a 1-dose vaginal [redacted] it also contains an external cream that can be used for up to 7 days.

Further, the sponsor appears to use two different names for this product. The name "One Dose Vaginal Yeast Infection Treatment" is listed in the first line of the text for the carton and educational brochure. The name "Vaginal Yeast Infection Treatment Combination Product" is used in the rest of the labeling for the carton and educational brochure. The name of the product should be the same in all portions of the labeling, and reflect that the product is a combination product.

2. Carton: Language and format for the back panel of the Vaginal Yeast Combination Product carton should be consistent with the "Drug Facts" version in Attachment 1 and with the final rule for OTC drug product labeling, published in the FEDERAL REGISTER of March 17, 1999, (64 FR 13254).

3. Educational Brochure: The Educational Brochure should be consistent with the carton and with the mock-up version in Attachment 1.



5. Suppository and Tube Labeling: No labeling was submitted for the suppository and tube. We recommend that the sponsor submit draft labels for these items. The labels should be drafted in a format similar to the suppository overwraps and tube labels of other recently approved MONISTAT products.

6. The sponsor should not place any other information in the labeling which may affect the blinding of this study.

7. In the FEDERAL REGISTER of March 17, 1999, (64 FR 13254), the Agency published a final rule to establish a standardized format for the labeling of OTC drug products. The final rule 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. In the final rule, headings and subheadings should be in bold type and upper and lower case letters, with pertinent information presented in a bulleted format. The Agency is also developing class labeling for all OTC vaginal antifungal products, which was discussed at an advisory committee meeting on September 11, 1998. When the OTC vaginal antifungal class labeling guidance is finalized, we recommend that the sponsor draft the labeling for all their OTC vaginal antifungal drug products according to the final guidance.

8. The reviewer's comments, recommendations, and copy of the attached labeling review may be forwarded to the sponsor.

/s/

Cheryl Turner, R.N., IDS

/s/

Helen Cothran, B.S., Team Leader

/s/

Linda M. Katz, M.D., M.P.H.

3/29/99

/s/

Ling Chin, M.D., M.P.H.

10 Pages
Redacted

DRAFT

LABELING



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

Received March 31, 1999.
Disk copy made for Phil.

March 30, 1999

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

AMENDMENT TO PENDING APPLICATION
Response to Reviewer Questions
Pending NDA 20-968
Miconazole Nitrate 1200 mg Vaginal [redacted] and 2% External Cream

Dear Dr. Goldberger:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream for treating vaginal candidiasis. Reference is also made to questions posed by the chemistry reviewer on March 22, 1999. At this time, Advanced Care Products (ACP) is responding to those questions and request that this information be made part of our pending application. In this submission, each question posed by the agency will be followed by ACP's response.

1. **In Vitro [redacted] Shell Disintegration/Rupture: Provide a complete and detailed description of the proposed methodology and conditions to determine [redacted] disintegration/rupture. Please include any development history of the method to assess disintegration/rupture.**

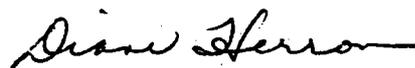
A complete and detailed description of the proposed methodology and conditions to determine ovule disintegration/rupture is described in document number AN-M-1761, Disintegration of Miconazole Nitrate (1200 mg) Vaginal [redacted] (Attachment I). This method follows the principle of USP method

[redacted]

This product was described in the Foreign Marketing History (within Item 2) and the Chemistry, Manufacturing and Controls section of the subject NDA. The Janssen method was chosen based on its ability to reproduce accurate results for the subject [redacted] and its history of long term use for [redacted]

We trust that this is a complete response to the questions posed. If you have any additional questions or require clarification, please feel free to contact me at (732)-524-1675.

Sincerely,



Diane Herron
Director, Regulatory Affairs

cc: Christina Chi, Project Manager, DSPIDP (HFD-590)

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

Desk Copy

C. Chi

February 18, 1999

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

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

MEETING PACKAGE

Pending NDA 20-968

Miconazole Nitrate Vaginal [redacted] and External Cream

Dear Drs. Goldberger and Bowen:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream for treating vaginal candidiasis. Reference is also made to our meeting request of January 12, 1999 to discuss the safety study protocol (98-006-P) and OTC switch requirements for the subject drug product. This meeting is slated for March 3, 1999 at 10:30 AM. At this time, Advanced Care Products (ACP) is submitting the meeting package for the subject meeting. Please note that the subject protocol is not included in this package as twenty-four copies have previously been sent to the participating divisions (DOTCDP, DSPIDP, DDMAC, DLNDC) on January 18, 1999.

Reference is also made to FDA's communication of November 5, 1998 regarding the status of the MONISTAT[®] 1 trade name for the subject pending NDA. ACP understands that this unresolved issue may impact the approval of the product under the User Fee Act. We are in the process of conducting extensive trade name research to address the FDA naming concerns while taking into account marketing strategies. In the near future, ACP will submit a naming proposal based on this research. While this is not a subject of the meeting, we felt that it was important to provide you the status of this critical issue.

If you have any questions, please feel free to contact me at (732)-524-1675. We look forward to a productive meeting.

Sincerely,

Diane M. Herron for

Diane Herron
Director, Regulatory Affairs

cc: Christina Chi, Project Manager, DSPIDP (HFD-590)
Elizabeth Yuan, Project Manager, DOTCDP (HFD-560)



Advanced Care Products

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

February 18, 1999

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

RE: MEETING PACKAGE
Pending NDA 20-968
Miconazole Nitrate Vaginal [redacted] and External Cream

Dear Christina Chi:

As per your request, enclosed, please seventeen (17) desk copies, which contain the meeting package materials for the meeting scheduled on March 3, 1999.

Should you have any questions on the information contained herein, please contact me directly at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron
Director, Regulatory Affairs



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

January 12, 1999

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

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

REQUEST FOR MEETING

Pending NDA 20-968

Miconazole Nitrate Vaginal [redacted] and External Cream

Dear Drs. Goldberger and Bowen:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole
trate [redacted] and 2% external cream for treating vaginal candidiasis. At this time, Advanced
Care Products (ACP) is beginning development of a program to provide for the eventual OTC
switch of the subject drug product. The cornerstone of this switch program is an OTC Actual
Use Study of the subject product.

We are therefore submitting for your review and comment a copy of the proposed protocol for
an Actual Use Study we are planning to begin early this year. At this time, we also wish to
request a meeting with the agency to discuss this protocol and the OTC switch requirements
for the subject drug product. I have also included a proposed meeting agenda which will be
finalized and submitted with full meeting materials two weeks before the scheduled meeting.

We do not anticipate that any of these discussions should affect the review of this product for
prescription use and fully intend to market this product by prescription upon approval. Please
feel free to contact me directly if you have any questions at (732) 524-1675.

Sincerely,

Diane Herron
Director, Regulatory Affairs

: Christina Chi, Project Manager, DSPIDP (HFD-590)
Sakineh Walther, Project Manager, DODP (HFD-560)

Proposed
Meeting Agenda

Protocol #98-006-p

Questionnaire

Duty Card



Advanced Care Products

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

October 8, 1998

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

**Amendment to
Original New Drug Application**

NDA 20-968

MONISTAT® 1 DUAL-PAK®
(miconazole nitrate 1200 mg soft gel
insert and miconazole nitrate 2%
external vulvar cream)

User Fee ID:

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application (NDA) 20-968 for miconazole nitrate 1200 mg soft gel insert and miconazole nitrate 2% external vulvar cream submitted June 30, 1998.

On September 24, 1998, an FDA pre-approval inspection was held at Advanced Care Products, 691 Route 1 South, North Brunswick, New Jersey, by Nancy Rolli, FDA Investigator from the North Brunswick Resident Post. During this inspection we agreed to amend the subject application to clarify the commitments we made regarding the Marketed Product Stability Program for the miconazole nitrate 1200 mg vaginal formulation.

Accordingly, we submit herewith an amended summary of our commitment (Vol. 1.3, p. 03-00658) as well as an amended Stability Protocol #TS-P-1296-2, entitled "Marketed Product Stability Monitoring of Miconazole Nitrate (1200 mg) Vaginal

(Vol. 1.3 p. 03-0006). Please note that the protocol commitments have not changed, we are only expanding the description of our intent for clarification.

Please replace these amended pages in the original application. We have numbered the pages the same as in the original submission, but added the suffix "A" to denote the amended pages.

This information is also being amended to the field copies sent to the San Juan, Puerto Rico; New Jersey; and Orlando, Florida FDA Field Offices.

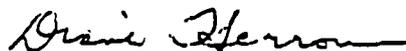
October 8, 1998
Page 2

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

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

ADVANCED CARE PRODUCTS



Diane Herron
Director, Regulatory Affairs

cc: Nancy Rolli
FDA Investigator
North Brunswick Resident Post

APPEARS THIS WAY
ON ORIGINAL

Advanced Care Products
Personal Products Company
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ORIGINAL

BZ

March 16, 1999



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

AMENDMENT TO PENDING APPLICATION

Response to Reviewer Questions

Pending NDA 20-968

Miconazole Nitrate 1200 mg Vaginal [redacted] and 2% External Cream

Dear Dr. Goldberger:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream for treating vaginal candidiasis. Reference is also made to questions posed by the chemistry reviewer on March 1, 1999. At this time, Advanced Care Products (ACP) is responding to those questions and request that this information be made part of our pending application. In this submission, each question posed by the agency will be followed by ACP's response.

1. Please submit the documentation from statistical analysis studies performed on at least three NDA stability batches. Confirm that the longest period of the stability testing at [redacted] for one batch PE 1341 (6 months for the other two batches: PE 1342 and PE1343). The stability data submitted in the NDA for the drug product do not support the requested expiration dating of 36 months.

Two reports of the statistical analyses for 1200 mg ovules produced with [redacted] (PE 1341, PE 1342, PE 1343) and [redacted] (SF063053, SF063058, SF068755) miconazole nitrate are included as Attachments 1 and 2, respectively. We do not confirm that the longest period of stability testing at 25°C/60% RH is 9 months for PE 1341 and 6 months for PE 1342 and PE 1343. At this time, the longest period of stability testing [redacted]

Reference Number (Miconazole Nitrate Source)	Number of months at 25°C/60% RH
PE 1341	18
PE 1342	18
PE 1343	18
SF 063053	12
SF 063058	12
SF 068055	12



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March 1, 1999

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

AMENDMENT TO PENDING NDA 20-968
Miconazole Nitrate 1200 mg Vaginal [redacted] and 2% External Cream

Dear Dr. Goldberger:

Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [redacted] and 2% external cream (proposed name "MONISTAT 1 Dual-Pak") for treating vaginal candidiasis. Reference is also made to November 5, 1998 fax from the CDER Labeling and Nomenclature Committee regarding the proposed proprietary name:

"While MONISTAT has long been associated with the ingredient miconazole nitrate, the earlier approved product MONISTAT 1 (containing tioconazole) established the precedent of associating single day therapy with tioconazole. Therefore, the currently proposed brand name is considered misleading." (copy attached)

At this time, Advanced Care Products (ACP) is proposing the following name change in response to FDA's concerns. ACP will change the tioconazole product's name to either MONISTAT TC or MONISTAT TL (based on which name the Nomenclature Committee finds preferable) as of September 1, 1999. This will be planned to coincide with the launch of the pending NDA product, MONISTAT 1 Dual-Pak (miconazole nitrate 1200 vaginal [redacted] and 2% external cream).

We are proposing this strategy at this time as we feel we have responded positively to the agency's concerns, conducted extensive research through a contract with [redacted]

[redacted] Using their methodology, ACP has determined that consumers can discern a difference between the proposed names and MONISTAT 1. In fact, many consumers (27-37%) notice that the difference is the active ingredient.

The subject amendment includes an Overview of the research conducted as well as a separate report from [redacted] which contains details of the findings.

ORIGINAL

Advanced Care Products

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

NEW CORRESP
NC

March 4, 1999

Karen Lechter
Jo Ann Spearmon
Food and Drug Administration
Division of Drug Marketing and Advertising Compliance (DDMAC)
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

RE: AMENDMENT TO PENDING NDA 20-968
Pending NDA 20-968
Miconazole Nitrate Vaginal and External Cream



Dear Ms. Lechter and Ms. Spearmon:

As per the request of Dr. Christina Chi, enclosed, please find one desk copy for each of you which contains information regarding the proposed proprietary name for the above-mentioned product. This information was submitted on March 1, 1999.

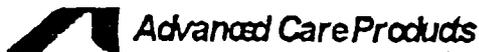
Should you have any questions on the information contained herein, please contact me directly at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

A handwritten signature in cursive script that reads "Diane Herron".

Diane Herron
Director, Regulatory Affairs



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

March 1, 1999

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

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

MEETING INFORMATION

Pending NDA 20-968

Miconazole Nitrate Vaginal [] and External Cream

Dear Drs. Goldberger and Bowen:

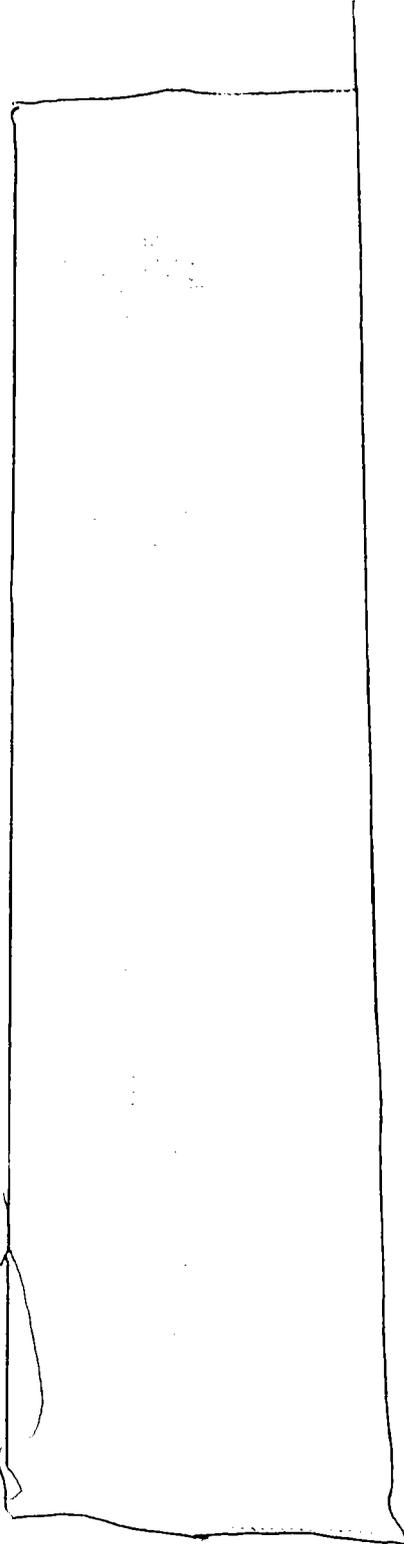
Reference is made to pending NDA 20-968 for the prescription use of a 1200 mg miconazole nitrate vaginal [] and 2% external cream for treating vaginal candidiasis. Reference is also made to a phone conversation of February 25, 1999 regarding a meeting scheduled for March 3, 1999, where clarification was requested on certain issues. At this time, Advanced Care Products (ACP) is submitting the clarifications requested for the subject meeting.

- 1) The proposed switch package was outlined in the draft NDA Table of Contents submitted on February 18, 1999. The protocol for the Consumer Usage Study (98-006-P) was submitted on January 12, 1999 (with 24 additional copies sent on January 18, 1999).
- 2) ACP would like to receive a response from FDA regarding the suitability of the proposed switch package, specifically if the proposed information (specified in the draft NDA Table of Contents) is adequate to fulfill FDA's OTC switch requirements. We would also like to receive feedback on the design of the safety study to ensure its appropriateness to address FDA concerns.
- 3) McNEIL Canada has recently received approval (February 5, 1999) for an identical product, a miconazole nitrate 1200 mg [] with 2% external cream (MONISTAT 1 Combination Pack) and also for the ovule only (MONISTAT 1 Vaginal [] for over-the-counter use. Copies of the approved package insert will be provided at the March 3 meeting.

**LIST OF REFERENCED APPLICATIONS IN NDA 20-968
(Attachment #2 to Form FDA 356b)**

Document Type and Number Title or Subject of Document Document Holder Volume/Page/Date

DRUG PRODUCT/COMPONENT MANUFACTURERS



**APPEARS THIS WAY
ON ORIGINAL**



Advanced Care Products

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

September 16, 1998

Dr. Christina Chi
Food and Drug Administration
Division of Special Pathogens and
Immunologic Drug Products (HFD-590)
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Christina Chi,

As per your request please find enclosed the cover letters sent with the reference articles for our microbiology section of NDA 20-968.

If you have any questions or need additional information please call me at 732-524-1675.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron
Director, Regulatory Affairs



Advanced Care Products

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

August 11, 1998

To: Food and Drug Administration
ATTN: Dorota Matecka, Ph.D., Chemistry Reviewer

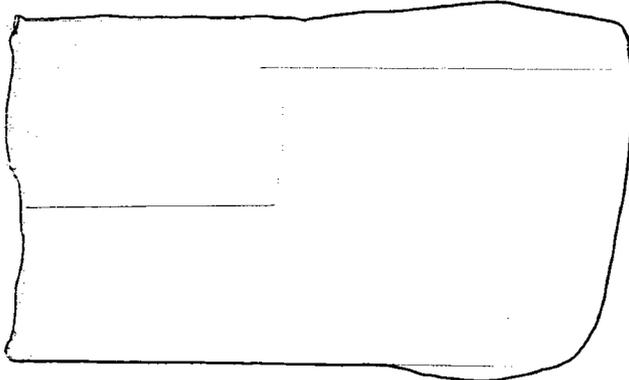
From: Diane Herron, Director Regulatory Affairs, Advanced Care Products-PPC

Re: NDA 20-968 (miconazole nitrate vaginal insert and 2% cream)

We confirm that the facilities on the attached two pages are the ONLY sites involved in manufacture, testing and packaging of drug substance and drug product for our NDA 20-969. We also confirm that they are ready for the GMP inspection.

There are only two sites that will be manufacturing miconazole nitrate drug substance for the MONISTAT[®]1 DUAL-PAK[®] product provided for in our NDA 20-968. They are as follows:

1.



2.

Sincerely,

ADVANCED CARE PRODUCTS

Diane Herron
Director, Regulatory Affairs

cc: Norman R. Schmuff, Ph.D., Chemistry Team Leader
Christina Chi, Ph.D., Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-968

Food and Drug Administration
Rockville MD 20857

Advanced Care Products
Attention: Ms. Diane Herron
Director, Regulatory Affairs
P.O. Box 6024
691 U.S. Route 1 South
North Brunswick, New Jersey, 08902-0724

AUG 10 1998

Dear Ms. Herron:

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

Name of Drug Product: Monistat® 1 Dual-Pak® Vaginal Cream
Therapeutic Classification: Antifungal
Date of Application: June 30, 1998
Date of Receipt: June 30, 1998
Due date: June 30, 1999
Our Reference Number: NDA 20-968

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

If you have any questions, please contact Dr. Christina H. Chi, Regulatory Health Manager, at 301- 827 - 2127.

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

Sincerely yours,

/S/

Ellen Frank, R.Ph.
Supervisor, Project Management Staff
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Date: 3/3/1999
Time: 10:30am
Location: Room S 300
9201 Corporate Blvd.
Rockville, MD 20851

Application: NDA 20-968, Monistat 1 Dual Pack, miconazole soft gel insert, [redacted] 1200mg with 2% external cream

Type of Meeting: Meeting for OTC switch requirements
Meeting Chair: Linda M. Katz, M.D., M.P.H.
Meeting Recorder: Elizabeth F. Yuan, R.Ph.

FDA Attendees, titles, and Office/Division:

Renata Albrecht, M.D., Deputy Division Director, HFD-590
Funmi O. Ajayi, Ph.D., Clin. Pharm./Biopharm Team Leader, HFD-880
Christina H. Chi, Ph.D., Project Manager, HFD-590
Ling Chin, M.D., M.P.H., Medical Officer, HFD-560
Phillip M. Colangelo, Ph.D., BioPharmaceutics Reviewer, HFD-880
Maria R. Cook, M.B.A., Supervisory Project Manager, HFD-560
Helen Cothran, Team Leader, HFD-560
Edward M. Cox, M.D., Medical Officer, HFD-590
Cheryl A. Dixon, Statistical Reviewer, HFD-725
Robert A. Eshelman, Compliance Officer, HFD-312
Linda L. Gosey, Microbiologist Reviewer, HFD-590
Kenneth L. Hasting, Pharmacology/Toxicology Team Leader, HFD-590
Linda M. Katz, M.D., M.P.H., Deputy Division Director, HFD-560
Brad G. Leissa, M.D., Medical Team Leader, HFD-590
Dorota M. Matecka, Ph.D., Chemistry Reviewer, HFD-590
William G. Nychis, Compliance Officer, HFD-312
Cheryl A. Turner, R.N., Interdisciplinary Scientist, HFD-560
Joseph K. Winfield, M.D., Medical Officer, HFD-590
Elizabeth F. Yuan, LTJG, R.Ph., Assistant Regulatory Mgmt. Officer, HFD-560

External Constituent Attendees and titles:

Frederick L. Cone, Manager, Clinical Research, Advanced Care Products
Diane Herron, Director, Regulatory Affairs, Advanced Care Products
Lynn Pawelski, Manager, Regulatory Affairs, Advanced Care Products
David Upmalis, Executive Director, Clinical, Advanced Care Products

Annette Stemhagen, Vice President, Strategic Development, Covance

Background: (Presented by Lynn Pawelski, Advanced Care Products)

- 1/26/98 meeting held between ACP and the agency (DSPIDP and DOTCDP)
- ACP decided to pursue Rx approval for Monistat 1 Dual Pack"
- NDA for Rx approval submitted on 6/30/98
- The name of the miconazole nitrate 1200 mg [redacted] for Rx is still pending the decision from the CDER's Labeling and Nomenclature Committee. (Submitted 11/5/98.)
- The OTC switch package will consist of a full safety update (with both US and Canadian data) a label comprehension study, and an actual use study.
- The development of the 600mg cream is still ongoing. Clinical efficacy on this product has yet to be determined.

Meeting Objective:

To provide information about or the specific reference to the proposed OTC switch package.

Discussion Points:

1. Actual Use Study Protocol:

- ACP will receive a formal review of the protocol.
- Recruitment- Advanced Care Products should ensure broad recruitment of subjects with vaginal symptoms, i.e. itching, burning, irritation, etc., who think they have a vaginal yeast infection. There was discussion of including all women with vaginal symptoms, with or without a previous vaginal yeast infection. Sponsor felt that the product is targeted only towards women with vaginal yeast infection, and the trial should reflect that.
- Methodology- the Agency reiterated that the sample should be demographically balanced including women from different geographic locations, literacy levels with an adequate sample of people at the low literacy levels. In addition, the Agency agrees with the inclusion of women less than 18 years of age.

It was emphasized that the name of the study physician should be provided in a non-directional manner. The consumers should not have any instruction as to when or why to contact the study physician.

Sponsor confirmed that the 1-800 number will be administered by Covance and is separate from the 1-800 # for Monistat Vaginal antifungal products.

- Statistical Analysis- the Agency proposed that there should be a statistical analysis plan for the comparison of adverse event rates in the actual use study to a historical control. The Agency expressed interest in determining a priori if safety differences (relative to the historical control) are noted, how the sponsor will determine whether this difference is significant or not. If significant, whether it would result in product specific safety labeling (that differs from "class labeling"). Advanced Care Products understood this

concern, and will check with their statisticians to see how the descriptive data from both Canada and US can be analyzed statistically.

- Use Patterns-
 - (i) The Agency inquired about the questions regarding consumer satisfaction with the product. Advanced Care Products ensured that this statement and others related to this subject, is included for improvement of product only, and will not be used for marketing claims. Sponsor also provided that the ratings of the quality of the interview will not be used to exclude subject records from data analysis.
 - (ii) The sponsor stated that the number of study subjects who drop out is minimized by a "pay as you go along" method.
 - (iii) The sponsor stated that the questionnaire was long because it lists the options for the recorder. The options, however, will not be given to the study subject. The responses to the questions will be recorded "verbatim".
 - (iv) Clarification was sought from the sponsor as to the wording of questions regarding use of the product with applicator. Sponsor clarified that in Europe the product is used without an applicator according to consumer preferences.
The agency provided feedback that those questions should be reexamined so the consumer is not confused over the use of the product by the phrase "with applicator".
 - (v) The Agency has suggestions for Advanced Care Products to improve their questionnaire. These suggestions will be available to Advanced Care Products by 2 weeks from meeting date.
- Diary Card-the Agency inquired about the definitions of the terms "mild, moderate, and severe". ACP is using these terms as perceived by the subject without further definition.

2. **Administrative issues:**

- The submission of this switch application is targeted for December 1999, and the pre-NDA meeting is targeted for September 1999. If this product seeks a complete switch, then it can be filed as a supplement to the approved NDA.
- The Actual Use Study will take about 4-6 months to complete.

Decisions (agreements) reached:

1. DOTCDP will supply Advanced Care Products with comments regarding the label and actual use study protocol.
2. The OTC switch application, either as new NDA or an efficacy supplement, is projected to be filed in 12/99.

3. A pre-NDA meeting is expected in 9/99. The preliminary results from the actual use study will be presented and discussed at this meeting.

Unresolved issues or issues requiring further discussion:

1. A document was filed with CDER's Labeling and Nomenclature Committee on March 1, 1999 by ACP for the renaming of Monistat 1 (tioconazole). The results are still pending.
2. The name of this 1200mg soft gel insert for Rx first, then OTC, will depend on the outcome of the document above.

Minutes Preparer: ey3/8, 3/23,4/7/1999

**APPEARS THIS WAY
ON ORIGINAL**

/S/
Chair Concurrence: J

Attachments/Handouts:
Monistat 1 Combination Pack, Canadian Label
Slides from ACP background Presentation

**APPEARS THIS WAY
ON ORIGINAL**