CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-538/S-006

CORRESPONDENCE

MENOREST MANUFACTURING, INC.

Via Federal Express

ORIGINAL

June 26, 1998

NDA SUPP AMEND
SCE-006 BRAL
006

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Revised 9/27/98

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS AMC 10/2/98 DATE

Re: NDA 20-538/S006 Amendment
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day

Dear Dr. Rarick:

Reference is made to the February 19, 1998 letter issued by your office which provided a review of the August 18, 1997 supplemental application (S006) to NDA 20-538. Menorest Manufacturing, Inc. hereby amends the subject SNDA to respond to all of the comments and requests for information. For each review, each comment/request is restated and followed by our response in **bold** type.

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Your prompt review of this information is appreciated.

Noted
ICR
10/2/98

Sincerely yours,

NOVEN PHARMACEUTICALS, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

11960 S.W. 144th Street, Miami, Florida 33186
Phone (305) 253-5099 Fax (305) 251-1887

MENOREST MANUFACTURING, INC.

ORIGINAL

Via Facimile Transmission
(hard copy via Federal Express)

March 19, 1998

John Markow
Food and Drug Administration
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 20 1998
HFD-580

SUPPL NEW CORRESP
SUF-006
SAC

Re: NDA 20-538/S-006
Estradiol Transdermal System
0.0375, 0.05, 0.075, and 0.10 mg/day

Dear Mr. Markow:

As per your telephone request of March 19, 1998 attached are the Case Report Forms from study 1012 showing the patch adhesion assessment. I have included a copy of the randomization schedule for the reviewer's convenience.

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

DL:cf

13300 S.W. 128th Street, Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

MENOREST MANUFACTURING, INC. ORIGINAL

Via Federal Express

March 3, 1998

SUPPL NEW CORRESP
S-006

3/17/98

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.L. ☐ MEMO
3/18/98
DATE

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-538/S-006

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby notifies the Food and Drug Administration of its intent to amend the above referenced application in accordance with 21 CFR 314.120(a)(1).

noted
3-17-98

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR - 4 1998
HFD-580

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

Enclosure
DL:cf

13300 S.W. 128th Street, Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

MENOREST MANUFACTURING, INC.

Via Federal Express

September 5, 1997

SUPPL NEW CORRESP

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 0 8 1997
HFD-580

Subject: **NDA 20-538**
Estradiol Transdermal System
0.0375, 0.05, 0.075, and 0.10 mg/day
[S-006]

Dear Dr. Rarick:

Menorest Manufacturing Inc., hereby amends the above referenced supplement with the following information:

1. The original formulation referenced in NDA 20-538 is not marketed in the United States.

2. The revised formulation will replace the original formulation referenced in NDA 20-538.

3. There is no trademark for the original product covered by NDA 20-538. Estradot™ (estradiol transdermal system) is the first trademark proposed for the product covered by this application.

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely yours,

NOVEN PHARMACEUTICALS, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

Attachment
DL:cf

11960 S.W. 144th Street, Miami, Florida 33186
Telephone (305) 253-5099 Facsimile (305) 251-1887

ORIGINAL

MENOREST MANUFACTURING, INC

SUPPL NEW CORRESP

Via Facsimile Transmission
(Hard copy via Federal Express)

Noted LCP 1/28/99

Noted 1/23/99

January 20, 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-538 - Supplement 006
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day
SUPPLEMENT - EXPEDITED REVIEW REQUESTED

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby confirms that it will use the tradename Vivelle®-Dot™ as approved on January 13, 1999 by the Labeling and Nomenclature Committee (confirmed in a conversation between Jennifer Mercier and David Lucking on January 18, 1999) for the product in the above referenced NDA.

In addition, Menorest Manufacturing, Inc. commits to manufacture product with printed backing two (2) months after the launch of the product described in the above referenced NDA. The backing will be printed with the tradename and the dosage strength as provided in our June 26, 1998 submission.

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 21 1999
HFD-580

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

DL:cf

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☒ MEMO
CSO INITIALS
DATE 1/29/99

11960 S.W. 144 Street ▲ Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

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ORIGINAL

MENOREST MANUFACTURING, INC

SUPPL NEW CORRESP

Via Federal Express

January 11, 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 12 1999
HFD-580

Re: NDA 20-538 - Supplement 006
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby submits the attached market research conducted by to support the approval of the trademark Vivelle®-Micro™ for the product referenced in the above NDA.

The following information is offered to address the Committee's statement that "micro" has long been associated with reduced dosing in oral contraceptives and for micronized drug substances.

The market research clearly demonstrates that the respondents associated micro with reduced size and not with reduced dosing in unaided testing. Fifty-seven (57%) associated the modifier "micro" with small. In addition, in order to emphasize the smaller size of Vivelle-Micro, the pouch and box will contain the words **"New! Smaller Patch, Same Strength"** for a period of 3 months after launch. (Refer to Attachment 1).

The second concern of the Committee was that "micro" has been associated with micronized drug substances. A product on the market, Micro-K, (A.H. Robins Company) is an oral dosage form containing micro encapsulated potassium chloride not micronized potassium chloride. In this case, micro is not associated with micronization but with micro encapsulation. In contrast, Vivelle®-Micro™ contains micronized estradiol. Therefore, even if the term "micro" was associated with micronized drug substances, this association would not be inconsistent with the micronized estradiol contained in Vivelle®-Micro™.

Therefore, Menorest Manufacturing, Inc. requests the Labeling and Nomenclature Committee consider the information presented above and in the market research (attached) when reconsidering approval of the trademark **Vivelle®-Micro™**.
Thank you for your consideration.

11960 S.W. 144h Street, Miami, Florida 33186
(305) 253-5099 ▲ (305) 251-1887

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

DL:cf

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

MENOREST MANUFACTURING, INC. SUPPL NEW CORRESP

Via Facsimile Transmission
(hard copy via Federal Express)

January 8, 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-538 (Supplement 006)
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, 0.10 mg per day

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby submits the following trademarks for the product referenced in NDA 20-538 Supplement 006 in the preferential order of consideration.

1. Vivelle-Dot
2. Vivelle-Ease

NDA 20-538 is identical in all respects to NDA 20-323 previously submitted by Noven Pharmaceuticals, Inc. and now owned by Novartis Pharmaceuticals Corporation. The product described in NDA 20-323 is marketed under the trademark **VIVELLE®**. After approval, NDA 20-538 will be transferred to Novartis Pharmaceuticals Corporation.

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Please contact me if you have any questions.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS ▲ DATE

CENTER FOR DRUG
REC'D
JAN 12 1999
HFD-580
EVALUATION AND RESEARCH

11960 S.W. 144th Street ▲ Miami, Florida 33186
Phone (305) 253-5000 ▲ Fax (305) 251-1887

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MENOREST MANUFACTURING, INC.

ORIGINAL

Via Facsimile Transmission
(hard copy via Federal Express)

SUPPL NEW CORRESP

January 7, 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 8 1999
HFD-

Re: Request for Meeting
NDA 20-538/S006 Amendment
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, 0.10 mg per day

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby requests a meeting with the Division of Reproductive and Urologic Drug Products to present research findings demonstrating that the trademarks Vivelle® and Vivelle®-Micro™ have a low potential of confusion among physicians, pharmacists, and post-menopausal women. The research was conducted by whose market research is designed to minimize error potential and assist in guiding the selection process of final tests names in accordance with "Patient Safety" Labeling and Nomenclature guidelines.

Those in attendance at the meeting will be myself and Mr. James L. Dettore, President, and

Thank you for your consideration.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking
Senior Director, Medical and Regulatory Affairs

11960 S.W. 144th Street ▲ Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

SLP 006 b

MENOREST MANUFACTURING, INC.

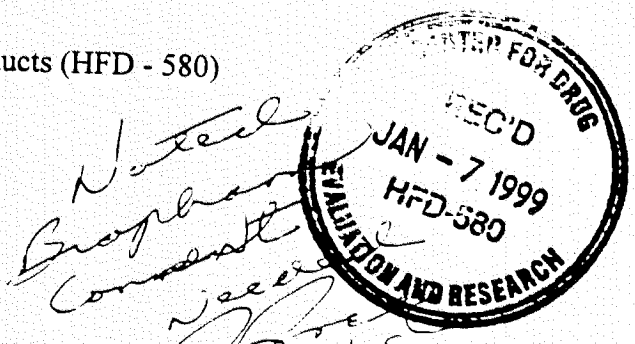
ORIGINAL

Via Federal Express

January 6, 1999

NDA SUPP AMEND

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-538/S006
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day

Dear Dr. Rarick:

Enclosed are the labeling changes requested by Jennifer Mercier on January 6, 1999.

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

1-12-99

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking
David Lucking
Senior Director, Medical and Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

11960 S.W. 144th Street, Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

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MENOREST MANUFACTURING, INC

Via Federal Express

ORIGINAL NEW CORRESP

December 8, 1998

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 9 1998
HFD-580

Re: NDA 20-538
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day

Dear Dr. Rarick:

Menorest Manufacturing, Inc. hereby submits the trademark **VIVELLE®-MICRO™** for the product referenced in NDA 20-538 Supplement 006.

NDA 20-538 is identical in all respects to NDA 20-323 previously submitted by Noven Pharmaceuticals, Inc. and now owned by Novartis Pharmaceuticals Corporation. The product described in NDA 20-323 is marketed under the trademark **VIVELLE®**. After approval, NDA 20-538 will be transferred to Novartis Pharmaceuticals, Inc.

In addition, Menorest Manufacturing, Inc. requests a meeting with the Labeling and Nomenclature Committee to present research findings demonstrating that the trademarks **VIVELLE® and VIVELLE®-MICRO™** have a low potential of confusion among physicians, pharmacists, and post-menopausal women. The research is being conducted by whose market research is designed to minimize error potential and assist in guiding the selection process of final test names in accordance with "Patent Safety" Labeling and Nomenclature guidelines.

Those in attendance at the meeting will be myself and Mr. James L. Dettore, President and C.E.O.

Thank you for your consideration.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking
Senior Director, Medical and Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS DATE

DL:cf

11960 S.W. 144h Street, Miami, Florida 33186
(305) 253-5099 ▲ (305) 251-1887

MENOREST MANUFACTURING, INC.

September 10, 1998

John Markow
Project Manager/CSO
Division of Reproductive and Urologic Drug Products (HFD – 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: FDA Request for Information
NDA 20-538/S006 Amendment
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, 0.10 mg per day

Dear Mr. Markow:

Pursuant to the telephone conversation between you, Dr. Mitra (Reviewing Chemist), and Menorest Manufacturing, Inc., the following information is provided to clarify the sample preparation and results reporting for the test procedure found on page 47 of the June 26, 1998 amendment for S006:

> Regarding test procedure for each finished product sample, two sample preparations are prepared. For each preparation, 5 units are placed in a single screw cap bottle and the units are then extracted according to the procedure. A single assay value is generated for each of the two preparations. The average of the two values is reported on the stability summary reports.

We consider this information proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 2 USC, Section 331j.

As discussed, will prepare a formal submission of this information. If you have any further questions or comments, you may contact David Lucking, Senior Director, Medical and Regulatory Affairs, at (305) 253-5099 extension 109.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

DL

MENOREST MANUFACTURING, INC.

NDA SUPPLEMENT
S-F30 6/182

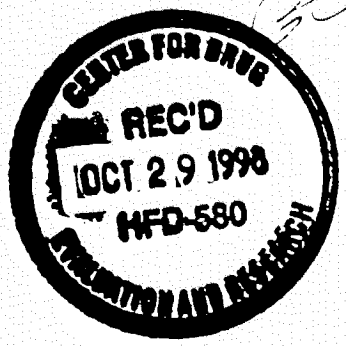
ORIGINAL

Reviewed & Letter to Sponsor
1/9/99
1/13/99

Via Federal Express

October 28, 1998

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857



Re: **NDA 20-538/S006**
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, and 0.10 mg per day

Dear Dr. Rarick:

Reference is made to the October 16, 1998 letter issued by your office which provided a review of the August 18, 1997 supplemental application (S006) to NDA 20-538 as well as the subsequent submissions dated March 19, June 26, and September 15, 1998. Menorest Manufacturing, Inc. hereby amends the subject SNDA to respond to all of the comments and requests for information. For each review, each comment/request is restated and followed by our response in **bold** type.

1-13-99

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Your prompt review of this information is appreciated.

Note
1/13/99

Sincerely yours,

MENOREST MANUFACTURING, INC.
David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs

NDA Ltr 1/14/99
See AP Ltr.

11960 S.W. 144th Street, Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

MENOREST MANUFACTURING, INC.

ORIGINAL

NDA SUPP AMEND

SCE-004 BL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS [illegible] 10/20/98 DATE

CENTER FOR DRUG REC'D SEP 16 1998 HFD-580 EVALUATION AND RESEARCH

September 15, 1998

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD - 580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: FDA Request for Information
NDA 20-538/S006 Amendment
Estradiol Transdermal System
0.0375 mg, 0.05 mg, 0.075 mg, 0.10 mg per day

Dear Dr. Rarick:

Reference is made to the June 26, 1998 amendment to the supplemental application (S006) to NDA 20-538 which was filed on August 18,1998. Menorest Manufacturing, Inc. hereby amends the subject SNDA to provide additional information at the request of the division as a result of a telephone conversation held on September 10, 1998 between Menorest Manufacturing and Mr. Markow (Project Manager/CSO) and Dr. Mitra (FDA Reviewing Chemist).

Pursuant to the telephone conversation, the following information is provided to clarify the sample preparation and results reporting for test procedure found on page 47 of the June 26, 1998 amendment for SNDA S006.

> Regarding Noven test procedure STP 309, for each finished product sample, two sample preparations are prepared. For each preparation, 5 units are placed in a single screw cap bottle and the units are then extracted according to the procedure. A single assay value is generated for each of the two preparations. The average of the two values is reported on the stability summary reports.

We consider all of the information contained in the application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

11960 S.W. 144th Street ▲ Miami, Florida 33186
Phone (305) 253-5099 ▲ Fax (305) 251-1887

If you have any further questions or comments, you may contact David Lucking, Senior Director, Medical and Regulatory Affairs, at (305) 253-5099 extension 109.

Sincerely yours,

MENOREST MANUFACTURING, INC.

David Lucking

David Lucking
Senior Director, Medical and Regulatory Affairs