CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-538/S-006

MEDICAL REVIEW(S)

Medical Officer's Summary of NDA Supplement

NDA 20-538/S006

JAN 8 1999

Name of Drug: Estradiol Transdermal System

Sponsor: Menorest Manufacturing, Inc.

Clinical Use: Estrogen replacement therapy (ERT)

Route of Administration and Dosage: Transdermal
0.0375mg, 0.50 mg, 0.075 mg, and 0.10 mg/day

Material Reviewed: FPL

Date of Submission: October 28, 1998

Comments:

The sponsor has responded to HFD-580 letter of October 16, 1998 requesting changes in the Chemistry, Pharmacokinetic, and Clinical sections of their label. Review of revised sections of the sponsor's label show the sponsor has complied with the requested changes, however, the Chemistry and Pharmacokinetic sections will make specific comments for their sections of the label. I will now comment on changes to the Clinical section of the label.

In the **Contraindications** section, the sponsor has added the following text to #5 of the label,

Comment: This change is acceptable and is based upon common clinical practice.

In the **Precautions** section, under **Hypercoagulability**, the sponsor has deleted the following two sentences,

These sentences have been replaced with the following,

Comment: The sponsor's proposed text is factual and is based on four reference articles in 1996 and 1997. It is clear that patients receiving estrogens are at a slightly increased

risk for venous thromboembolism (VTE). This increase risk is about 1 to 3 additional cased of VTE per 10,000 women years. These reference studies are larger studies than previously reported studies, and have greater diagnostic certainty than in earlier years. Therefore, the proposed text is acceptable with the following modification,

However, please note HFD-580 has drafted the following text in the **Guidance Document for ERT**:

In the Patient Package Insert (PPI) the sponsor has inserted the following change:

Guidance Document for ERT, which states the following:

Recommendation:

The sponsor's proposed changes are acceptable and are consistent with other sponsor's revised labeling. However, the sponsor should be informed of the drafted Guidance Text, which are similar to the proposed text, but are more complete and understandable to the patient. It is strongly recommended that the sponsor adopt the ERT guidance document text once FDA formally approves it.

/S/

Phill H. Price, M.D.
January 7, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-538/S-006

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS

CHEMIST'S REVIEW #3

JAN 5 1999

1. NDA NUMBER: 20-538

2. NAME AND ADDRESS OF APPLICANT
Menorest Manufacturing Inc.
11960 144th Street
Miami, Florida 33186

3. SUPPLEMENT NUMBER/DATE/DATE RECEIVED
SCS-006/8/18/97/8/19/97; SCS-006, SNC/9/5/97/9/8/97

4. NAME OF THE DRUG: Tradename was not provided
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: New formulation with various strengths based on surface area differences.
7. AMENDMENTS/REPORTS/ DATE: NDA 20-538, SCF-006/BZ/10-28-98/10-29-98
8. PHARMACOLOGICAL CATEGORY
Estrogen/HRT

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
NDA 20-323 (Vivelle)
11. DOSAGE FORM : Transdermal
12. POTENCY
0.0375 mg/day (3.75 cm^2), 0.05 mg/day(5 cm^2), 0.075 mg/day (7.5 cm^2), and 0.1 mg/day(10 cm^2)

13. CHEMICAL NAME AND STRUCTURE
$C_{18}H_{24}O_2$
MW = 272 .4

Estra-1,3,5(10)-triene-3,17β-diol

14. COMMENTS

The supplement SCS-006 was reviewed on 2-12-98 and it was not approved because of several deficiencies. The sponsor provided the responses to those deficiencies. The deficiencies and the review of the deficiencies were conducted in Chemistry Review #2, dated 9-28-98. Based on the review an approvable letter was sent on 10- 18- 98 with information request. The information requested, responses to the information requested followed by the reviewer comments are provided

The following changes were made:

Responses to the information request were made.

CONCLUSIONS AND RECOMMENDATIONS:

With regard to CMC the application can be approved. However, the labeling issues should be reviewed by the Medical and Biopharmaceutics Reviewers, and the labeling should be found satisfactory before this application can be approved.

/S/

Reviewed By: Amit K. Mitra, Ph.D, 1-5-99

/S/ 1/5/99

R/D INIT BY: Moo-Jhong Rhee, Ph.D

CC: A. K. MITRA/HFD-580
M.J.RHEE/HFD-580
J. Mercier/HFD-580
NDA 20-538

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS

CHEMIST'S REVIEW #2

1. NDA NUMBER: 20-538

2. NAME AND ADDRESS OF APPLICANT
Menorest Manufacturing Inc.
11960 144th Street
Miami, Florida 33186

3. SUPPLEMENT NUMBER/DATE/DATE RECEIVED
SCS-006/8/18/97/8/19/97

SCS-006, SNC/9/5/97/9/8/97

4. NAME OF THE DRUG: Tradename was not provided
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: Response to the deficiencies for supplement SCS-006
7. AMENDMENTS/REPORTS/ DATE: NDA 20-538, SCF-006BC/6/26/98/6/29/98

SCF-006BC/9-15-98/9-16-98

8. PHARMACOLOGICAL CATEGORY
Estrogen/HRT

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
NDA 20-323 (Vivelle)

11. DOSAGE FORM : Transdermal

12. POTENCY
0.0375 mg/day (3.75 cm^2), 0.05 mg/day(5 cm^2), 0.075 mg/day (7.5 cm^2), and 0.1 mg/day(10 cm^2)

13. CHEMICAL NAME AND STRUCTURE
$C_{18}H_{24}O_2$
MW = 272 .4

Estra-1,3,5(10)-triene-3,17β-diol

14. COMMENTS

The supplement SCS-006 was reviewed on 2-12-98 and it was not approved because of several deficiencies. The sponsor provided responses for those deficiencies.

The following changes were made:

Responses to the deficiencies recorded in SCS-006 were provided.

CONCLUSIONS AND RECOMMENDATIONS: The application is approvable pending the following deficiencies.

a. Based on the quality control data and considering manufacturing variability the specification for vinyl acetate should be [redacted] ppm instead of [redacted] ppm. The specification sheet should be updated with the new specification.
b. Based on the stability data provided a tentative shelf life of 24 months can be granted. The sponsor is reminded to include release liner peel force and adhesion strength parameters as a part of post approval commitment.
c. The storage condition in the text of "How Supplied" section should be changed from to to be consistent with the pouch and carton label.
d. No Tradename for the drug product was provided. Once the Tradename is selected and approved through a prior approval supplement, the actual representation of the Tradename on the printed label should be submitted.

The responses to the deficiencies noted by the Biopharmaceutics reviewer should be reviewed by the Biopharmaceutics Reviewer and those deficiencies should also be found satisfactory before this application can be deemed approvable.

/S/

Reviewed By: Amit K. Mitra, Ph.D, 9-28-98

/S/ 9/24/98

R/D INIT BY: Moo-Jhong Rhee, Ph.D

CC: A. K. MITRA/HFD-580
M.J.RHEE/HFD-580
J. Markow/HFD-580
NDA 20-538

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS CHEMIST'S REVIEW

1. NDA NUMBER: 20-538

2. NAME AND ADDRESS OF APPLICANT
Menorest Manufacturing Inc.
11960 144th Street
Miami, Florida 33186

3. SUPPLEMENT NUMBER/DATE/DATE RECEIVED
SCS-006/8/18/97/8/19/97

SCS-006 SNC/9/5/97/9/8/98

4. NAME OF THE DRUG: Estradiol Transdermal system)
5. NONPROPRIETARY NAME: Estradiol Transdermal System
6. SUPPLEMENT PROVIDES FOR: New formulation with various strengths based on surface area differences.
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY
Estrogen/HRT

9. HOW DISPENSED
Prescription

10. RELATED IND/NDA/DMF/SUPPLEMENT
20-323
11. DOSAGE FORM : Transdermal
12. POTENCY
0.0375 mg/day (3.75 cm^2), 0.05 mg/day(5 cm^2), 0.075 mg/day (7.5 cm^2), and 0.1 mg/day(10 cm^2)

13. CHEMICAL NAME AND STRUCTURE
$C_{18}H_{24}O_2$
MW = 272 .4

Estra-1,3,5(10)-triene-3,17β-diol

14. COMMENTS

The estradiol transdermal system is a drug in adhesive transdermal system where estradiol is dispersed in a new adhesive formulation. The revised formulation contain less amount of estradiol(0.16 mg/ cm^2 vs. original 0.3 mg/cm^2) delivers the same amount of estradiol over 3.5 days. To support this change the following comparison between the approved and the current formulation has been made:

1. Qualitative and Quantitative composition
2. Comparison of drug product specifications
3. Comparison of analytical methods
4. Comparison of equipment
5. Comparison of process

The following changes were made:

1. Formulation composition has been changed qualitatively and quantitatively.

15. CONCLUSIONS AND RECOMMENDATIONS: The approval for the requested change in the formulation can not be granted until all the deficiencies are corrected.

/S/

Reviewed By: Amit K. Mitra, Ph.D, 2-12-98

R/D INIT BY: Moo-Jhong Rhee, Ph.D /S/ 2/12/98

CC: A. K. MITRA/HFD-580
M.J.RHEE/HFD-580
J. Markow/HFD-580
NDA 20-538