CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-538/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ORIGINAL

OCT - 2 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-538 Suppl. 006
Drug:	Estradiol Transdermal System (0.0375, 0.05, 0.075, and 0.10 mg/day)
Sponsor:	Menorest Manufacturing, Inc.
Date of Submission:	3/19/98, 6/26/98
Type of Submission:	Revised Labeling
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

The original NDA for this product was approved on 07/31/96. NDA 20-538/S006 was submitted on 08/18/97 to support changes in the formulation and the size of etsradiol transdermal patches (see biopharm review in Attachment I). Subsequently, following the review of the submission dated 08/18/97, the sponsor submitted the following information to the supplemental NDA:

- case report forms from study 1012 showing the patch adhesion assessment on 3/19/98 in response to the FDA's request via telephone on 3/19/98.
- revised labeling and some chemistry information in response to the FDA's letter of request dated 2/19/98 (Attachment II).

Reviewer Comments:
The adhesion data submitted in case report forms support the previously reviewed mean data and are acceptable. However, it should be noted that 100% adhesion reported in these data is rather unusual for transdermal patches. Since the adhesion data collected in the bioequivalence study is for a small number (11) of patients, it does not support any labeling claim.

Labeling Comments:
The pharmacokinetics section of the proposed labeling should be revised as follows:

Pharmacokinetics:
[Please include the first paragraph of Pharmacokinetics section from the current approved label with last sentence removed.]

Absorption
[Please include the second paragraph of Pharmacokinetics section regarding the multiple dose study and the figure and table for steady state levels from the current approved label.]

[The following statement regarding the formulation change should be included at the end of Absorption section.]
The original formulation that was tested in clinical trials has been revised to reduce the patch sizes and the revised formulation was shown to be bioequivalent to the original formulation.

The last sentence in the Distribution section should be revised to include the closing parentheses.

No changes are recommended in Metabolism, Excretion, Special Populations and Drug Interaction sections.

The Adhesion section must be deleted because the adhesion data collected in the bioequivalence study is insufficient to support this statement.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the adhesion data and the revised labeling submitted to NDA 20-538/S006 dated 3/19/98, 6/26/98. The revised labeling is acceptable provided the sponsor addresses the labeling comments outlined above appropriately.

Please convey the Recommendation and Labeling Comments to the sponsor as appropriate.

/S/ 9/2/98
Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT initialed by Ameeta Parekh, Ph.D., Team Leader /S/ 9/2/98

cc: NDA 20538/S006, HFD-580 (Price, Markow), HFD-870 (M.Chen, Parekh), CDR (B.Murphy for Drug).

ATTACHMENT I
(Biopharm Review dated 2/17/98)

FEB 17 1998

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-538 Suppl. 006
Drug:	Estradiol Transdermal System (0.0375, 0.05, 0.075, and 0.10 mg/day)
Sponsor:	Menorest Manufacturing, Inc.
Date of Submission:	08/18/97
Type of Submission:	Bioequivalence Study (New Formulation)
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

On August 18, 1997, Menorest Manufacturing, Inc. submitted supplement 006 to NDA 20-538 for Estradiol Transdermal System (ETS). The original NDA was approved on July 31, 1996. In this supplement, the sponsor is providing data to support the approval of a revised formulation which consists of lower concentration of estradiol in a modified adhesive system. The quantitative composition of the old and new formulations is included in Attachment I. According to the sponsor, the modified system fluxes at a higher rate per unit area thereby allowing a smaller unit size while maintaining equal delivery over the 3.5 day wear period. The four equivalent dosages of the new formulation for which, the approval is sought are as follows:

Strength	SecondGeneration (New)	First Generation (Old)
0.0375 mg/day	0.585 mg/3.75 cm^2 unit	3.28 mg/11 cm^2 unit
0.05 mg/day	0.780 mg/5 cm^2 unit	4.33 mg/14.5 cm^2 unit
0.075 mg/day	1.17 mg/7.5 cm^2 unit	6.57 mg/22 cm^2 unit
0.10 mg/day	1.56 mg/10 cm^2 unit	8.66 mg/29 cm^2 unit

To support the approval of the revised formulation (referred to as Noven Second Generation ETS), the sponsor provided bioequivalence data between the largest approved patch, 29 cm^2, and the proposed new 10 cm^2 and 5 cm^2 patches; proposed *in vitro* release method and specification; comparative *in vitro* skin permeation data between the existing and the new formulation; and the revised labeling.

Bioequivalence

Study 1012 was conducted to investigate the bioequivalence between the 29 cm^2 patch (approved formulation) and the 10 cm^2 patch of revised formulation. A synopsis of the study report is included in Attachment II. Twelve post-menopausal, healthy women were enrolled in this open-label, single-center, single dose, randomized, three-treatment, three-period crossover study. The

subjects, according to the randomization schedule, applied the following three patches on three separate occasions , each separated by one week wash out period:

Treatment A: One 5 cm^2 Noven Second Generation ETS (deliver 0.05 mg/day)
Treatment B: One 10 cm^2 Noven Second Generation ETS (deliver 0.10 mg/day)
Treatment C: One 10 cm^2 Noven First Generation ETS (deliver 0.10 mg/day)

The pharmacokinetic parameters for E_2 and E_1 following the Treatments of A, B, and C along with 90% confidence intervals estimated from two one-sided t-test analysis using ANOVA model are summarized in Table 1:

Table 1. Mean (SD) pharmacokinetic parameters of Estradiol and Estrone (n=11)*

Parameter	Treatment A	Treatment B	Treatment C	90% CI for B/C**
Estradiol				
C_{max} (pg/ml)	54.8 (13.9)	106.2 (35.9)	101.6 (39.1)	94.23 – 120.09
$AUC_{(0\text{-}108h)}$	3678 (1032)	6409 (2516)	6498 (1788)	83.76 – 106.23
$AUC_{(0\text{-}\infty)}$	3970 (860)	6972 (2190)	6590 (1788)	85.80 – 109.22
T_{max} (h)	34.9 (19.5)	29.5 (19.6)	27.3 (20.1)	
Apparent Dose (mg/day)	0.066 (0.02)	0.131 (0.06)	0.151 (0.03)	
Estrone				
C_{max} (pg/ml)	75.6 (15.1)	97.0 (27.0)	98.3 (21.2)	89.73 – 106.78
$AUC_{(0\text{-}108h)}$	4662 (996)	6270 (1777)	6294 (1406)	90.87 – 106.66
$AUC_{(0\text{-}\infty)}$	5740 (1251)	7616 (2034)	7588 (1669)	92.39 – 107.26
T_{max} (h)	58.9 (12.5)	45.8 (22.0)	48.0 (18.6)	

* One oultier (Subject # [redacted]) was excluded from the data analysis
* *90% Confidence intervals estimated from log transformed parameters

When the two one-sided test analysis was performed with all 12 subjects data from treatments B and C, the 90% CI for all parameters of estradiol and estrone except for C_{max} of estradiol were within the agency's required % range. However, the 90% CI for C_{max} of estradiol ( ) was slightly out of the required interval. An outlier test (Hawkins one-tailed test for single outlier) was conducted to examine for the presence of any outlier in the ratios of estradiol C_{max}. Using the outlier test, the sponsor concluded that the B/C ratio of C_{max} for subject was an outlier. As shown in Table1, when the data was reanalyzed by excluding the subject , the 90% CI for all parameters are within the agency's acceptable range.

Reviewer Comments:

1. The 90 % CI for all required parameters of estradiol and estrone estimated from all 12 subjects' data are within the % interval except for the C_{max} of estradiol which is slightly exceeding the upper limit. When the data was reanalyzed by excluding the outlier

subject, the CI were within the acceptable interval. Therefore, it can be concluded that the 10 cm^2 New Second Generation ETS is bioequivalent to 29 cm^2 First generation ETS.

2. It should be noted that the sample size of the study (n=12) is little less than the required sample size (n=14 to 16) to detect 20% difference with 80% power. However, since the difference is only small, the bioequivalence results are acceptable.

3. There was no statistically significant difference among the dose normalized C_{max} and AUC of estradiol for 5 cm^2, and10 cm^2 new patches suggesting that 5 cm^2 and 10 cm^2 are dose proportional with respect to estradiol. However, the two sizes are not dose proportional with respect to estrone levels.

***In Vitro* Dissolution**

The proposed product dissolution method and specifications are as follows:

Apparatus Type:
Medium:
Volume:
- 3.75 cm^2 unit
- 5.00 cm^2 unit
- 7.5 cm^2 unit
- 10.9 cm^2 unit

Speed of Rotation:
Sampling Times:

Specifications:

Sampling Time	% Label Claim
2 hr	
4 hr	
6 hr	

The *In Vitro* release data for the lots used in bioequivalence study is summarized in the following Table:

Table 2: % of Label Claim dissolved from the bio-lots

Unit Size	Lot Number	% Label Claim		
		2 Hour	4 Hour	6 Hour
3.75 cm^2	6G1201-E7			
5.0 cm^2	6G1201-E3*			
7.5 cm^2	6G1201-E5			
10 cm^2	6G1201-E2*			

* Lots used in bioequivalence study.

Reviewer Comments:

1. The results outlined in Table 2 indicate that the *in vitro* release rates are similar for all the different size patches studied.

2. The proposed dissolution method is the same as the approved method for the existing formulation. But the proposed specifications are different and considered wide. The release specifications should be set as mean release rates at 2, 4, and 6 hours of the bio-lots ± 10% of label claim. Therefore, based on the *in vitro* release data for the lots used in bioequivalence study, it is recommended that the following specifications be adopted for the revised formulation.

Recommended specifications:

2 hr
4 hr
6 hr

***In Vitro* Skin Permeation Data:**

The sponsor conducted a study to compare the percutaneous penetration of estradiol through human cadaver skin from Noven's first and second generation patches using an *in vitro* diffusion cell system. The summary of the study results are included in Attachment III. The results of this study showed that

I) The skin permeation rate of estradiol from second generation patch was on average 2.9 times that of the first generation patch.

II) The skin permeation rates of estradiol from the Noven first and second generation patches are similar when normalized to the patch sizes.

Adhesion and Skin Irritation Data:

The protocol for the bioequivalence study included a plan to evaluate the patch adherence at 2, 4, 8, and then at every 12 hours after application of the patch. The sponsor stated that tansdermal patch fell off in the shower for the subject in period III (Treatment C: Reference patch) and was replaced immediately without any tape. Except this incident, it is reported that all patches adhered well and did not require taping for all three periods.

In addition, the local skin irritation was subjectively evaluated immediately and at 24 hours following removal of the patch. The skin irritation data is included in Attachment IV. The results showed that there was no significant irritation for the majority of the patients (9 out of 12) in Treatment groups A and B, while 7 patients out of 12 in Treatment group C had mild erythma.

Reviewer Comment:

It should be noted that even though the sponsor stated that the transdermal patches adhered well during all three periods of treatment, no data was provided to support this statement. The sponsor, in response to the request by this reviewer, provided a Table of adhesion data which is not satisfactory. Therefore, it is recommended that the sponsor provide all the patient case report forms containing adhesive information for the bioequivalence study.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) has reviewed the supplement No. 006 to NDA 20-538 dated 08/18/97. OCPB/DPE II is of the opinion that the bioequivalence data submitted in study 1012 is acceptable and the new second generation formulation is considered bioequivalent to the approved first generation formulation. However, before the supplement is approved, the sponsor should address the following deficiencies and/or comments:

1. It is recommended that the dissolution specifications be modified as follows:
   2 hr
   3 hr
   4 hr

2. Complete adhesion data including the patient case report forms collected in the bioequivalence study should be submitted for review.

3. Regarding the labeling, it is recommended that the sponsor include the multiple dose pharmacokinetic data from the original formulation in the labeling and add the single dose data obtained in bioequivalence study. Additionally, the Clinical Pharmacology section of the label should be reformatted according to the division internal guidelines (see Attachment IV).

Please convey the Recommendation and Comments 1 through 3 to the sponsor as appropriate.

S 2/17/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Angelica Dorantes, Ph.D. KGB 2/17/98

FT signed by Angelica Dorantes, Ph.D. /S/ 2/17/98

cc: NDA 20538/S006, HFD-580 (Price, Moore), HFD-870 (M.Chen, Dorantes, Jarugula), CDR (B.Murphy for Drug).

ATTACHEMNET II
(Sponsor's Revised Labeling)

Redacted 15

pages of trade

secret and/or

confidential

commercial

information

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-538 Suppl. 006
Drug:	Estradiol Transdermal System (0.0375, 0.05, 0.075, and 0.10 mg/day) JAN 7 1999
Sponsor:	Menorest Manufacturing, Inc.
Date of Submission:	10/28/98
Type of Submission:	Revised Labeling
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

On August 18, 1997, Menorest Manufacturing, Inc. submitted supplement 006 to NDA 20-538 for Estradiol Transdermal System (ETS) to seek approval for a revised formulation (with reduced patch sizes) which consists of lower concentration of estradiol in a modified adhesive system. The original NDA was approved on July 31, 1996. The revised formulation was shown to be bioequivalent to the original approved formulation (see biopharm reviews dated 02/17/98 and 10/02/98). In the current submission dated 10/28/98, the sponsor has responded to the Agency's comments and request for information.

Comment:
The sponsor's has adequately addressed the Agency's comments on the Clinical Pharmacology section of the labeling.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) has reviewed the supplement No. 006 to NDA 20-538 dated 10/28/98. The sponsor's has adequately addressed the Agency's comments on the Clinical Pharmacology section of the labeling and the supplement is recommended for approval from OCPB perspective.

/S/ 1/5/99
Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D. /S/ 1/7/99

FT signed by Ameeta Parekh, Ph.D. /S/ 1/7/99

cc: NDA 20538/S006, HFD-580 (Price, Mercier), HFD-870 (M.Chen, Parekh, Jarugula), CDR (B.Murphy for Drug).

SPONSER'S RESPONSE:

Labeling

CLINICAL PHARMACOLOGY section

The **Pharmacokinetics** subsection of the proposed labeling should be revised as follows:

1. The first paragraph in the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, should be the same as that in the currently approved package insert. However, the last sentence should be deleted. Therefore, this paragraph should read:

Response

The first paragraph of the CLINICAL PHARMACOLOGY section Pharmacokinetics subsection has been revised as requested.

2. *Absorption* subsection

   This subsection should be replaced with the following:

   a. The second paragraph regarding the multiple-dose study that begins, and the figure and table for steady state levels from the currently approved label should be included.

   b. The following sentence should be added as the last sentence:

Response

The *Absorption* subsection has been revised as requested.

3. *Distribution* subsection

The last sentence should be revised to include the closing parentheses so that the sentence reads, "However, following three months transdermal estradiol administration (100 μ/day) normal physiologic distribution of estradiol and estrone in peripheral plasma fractions (free, albumin-bound, and SHBF-bound was maintained) (*Maturitas.* 1988; 10:267 to 269).

Response

The last two sentences have been removed. These sentences were in the CombiPatch™ draft labeling (NDA 20-870) but subsequently removed from the final printed labeling. Therefore, we propose to remove them from this section. In addition, the sentence that begins to the end of the paragraph has been removed since this information referred to a table that the Agency requested be removed in point 2a.

4. The sections *Metabolism, Excretion, Special Populations, and Drug Interactions* are acceptable.

Response

No response required.

5. *Adhesion* subsection

This section must be deleted because the adhesion data collected in the bioequivalence study is insufficient to support this statement.

Response

The *Adhesion* subsection has been deleted as requested.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-538/S-006

ADMINISTRATIVE DOCUMENTS

Teleconference Minutes

Date: January 22, 1999 **Location:** Parklawn; 17B-45

NDA 20-538/S-006 **Drug:** Vivelle® Dot™ **Indication:** HRT

Sponsor: Menorest Manufacturing, Inc.

Meeting Chair: Jennifer Mercier, Project Manager

FEB 9 1999

External Lead: David Lucking, Senior Director, Medical and Regulatory Affairs

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Jennifer Mercier, Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP); HFD-580

External Attendees:
David Lucking, Senior Director, Medical and Regulatory Affairs, Menorest Manufacturing, Inc.

Meeting Objective: To confirm tradename selected by the sponsor and approved by the LNC, and to propose a commitment to printed backing two months after the launch of the product.

Background:

- the sponsor requested that they be granted the ability to manufacture their approved product for two months without printed backing
- discussion between Dr. Rhee, Chemistry Team Leader and Dr. Mitra, Review Chemist concluded that this was acceptable with the Division Director's concurrence.
- Drs. Mitra and Rhee requested that a Prior Approval supplement be submitted to the NDA with the labeling changes and with the lot numbers identified the batches that will not have the printed backing
- Dr. Rarick, Division Director, is aware that they will manufacture their product without printed backing for two months
- the sponsor was notified in this teleconference that they would have to submit a Prior Approval supplement containing the labeling changes and the lot numbers of the batches that would not have the printed backing on them

Action Items: None

/S/

Minutes Preparer

/S/ 2/5/99

Concurrence, Chair

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Rumble/Pauls/Mercier
HFD-580/Rarick/Rhee/Mitra

drafted: Mercier, February 3, 1999
concurrence:
final:

MINUTES