

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-870**

**CHEMISTRY REVIEW(S)**

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)**  
**REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS**

**NDA # 20-870**                      **Chemistry Review # 1**                      **Review Date: 7-14-98**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
Original	8-07-97	8-08-97	08-13-97
Amendment	10-28-97	10-29-97	10-29-97
Amendment	12-04-97	12-05-97	12-05-97
Amendment	2-11-98	2-11-98	2-11-98
Amendment	6-23-98	6-24-98	6-24-98

**NAME AND ADDRESS OF APPLICANT**

Rhone-Poulenc Rorer Pharmaceuticals, Inc.  
500 Arcola Road  
Collegeville, PA 19426

**DRUG PRODUCT NAME**

Proprietary: Combipatch  
Non-proprietary/USAN: Estradiol/Norethindrone acetate Transdermal System  
(E2/NETA Transdermal System)  
Compendium: does not apply  
Code name/number: None  
Chem. Type/Ther. Class: 3 S

**ANDA SUITABILITY PETITION/DESI/PATENT STATUS:** N/A

**PHARMACOL. CATEGORY/INDICATION:** Combination estrogen/progestin, Hormone replacement in post menopausal women.

**DOSAGE FORM:** Transdermal Delivery System

**STRENGTHS:** 1) 50 mcg E2 and 140 mcg NETA; 2) 50 mcg E2 and 250 mcg NETA

**ROUTE OF ADMINISTRATION:** Transdermal (twice weekly application)

**Dispensed:** By prescription

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:**

Estradiol- Estra-1,3,5(10)-triene-3, 17-diol (17  $\beta$  ); Estra-1,3,5(10)-triene-3, 17  $\beta$  -diol;  
Norethindrone acetate- 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy), (17  $\alpha$ )

$C_{18}H_{24}O_2/C_{22}H_{28}O_3$  (Estradiol/Norethindrone Acetate)  
272.39/340.47

SUPPORTING DOCUMENTS: DMF

DMF  
DMF  
DMF  
DMF  
DMF

DMF

APPEARS THIS WAY  
ON ORIGINAL

Type/No.	Subject	Holder	Status	Review Date	Letter Date
DMF	Estradiol		Adequate	2-26-98	NA
DMF	Estradiol		Adequate	1-22-98	NA
DMF	Norethindrone acetate		not adequate	6-4-98	6-4-98
DMF	Norethindrone acetate		adequate	6-10-98	NA
DMF			adequate (	7-7-98	NA
DMF			adequate	6-29-98	NA
DMF			Adequate based on NDA 20-489 review by H. Davies	5-22-95 (see review notes)	NA
DMF	Composite film		Adequate based on NDA 20-323 review by H. Davies	6-4-93 (see review notes)	NA

RELATED DOCUMENTS

NDA 20-489 (Theratech, Inc.), NDA 20-323 (Noven Pharmaceuticals), IND  
(Rhone-Poulenc Rorer Pharmaceuticals)

CONSULTS

1. The proposed trademark "CombiPatch" was sent to the labeling and nomenclature committee on 2-18-98. The trademark CombiPatch is acceptable.
2. The EER was sent on 1-15-98. The inspection results are satisfactory

REMARKS/COMMENTS

The application was declared fileable contingent on stability data analysis is available. The amendment dated 12-04-97 contains stability data analysis. The initial tradename ALIATIS was submitted in the NDA 20-870. In an amendment to this NDA, dated 2-11-98, the sponsor requested that the tradename be changed to Combipatch. On 3-06-98 the LNC suggested that there are no misleading aspect with Combipatch. The division accepted the LNC's recommendation and the tradename Combipatch was accepted. The firm requested a categorical exclusion from environment assessment based on EIC less than 1 ppb in an amendment dated 10-28-97. The amendment dated 2-11-98 contains updated labeling information. The amendment dated 6-23-98 contains printed labels.

CONCLUSION AND RECOMMENDATIONS

With regard to chemistry, manufacturing and controls, the application is approvable pending some additional information and changes.

cc: NDA original  
HFD-580/A. K. Mitra/  
HFD-580/M. J. Rhee, Ph.D  
HFD-580/J. Markow  
HFD-580/Div. File  
R/D Init. By

7/14/98

/S/

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Amit K. Mitra, Ph.D

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)**  
**REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS**

**NDA # 20-870**                      **Chemistry Review # 2**      **Review Date: 7-31-98**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
Amendment	7-15-98	7-15-98	7-17-98
T-Con Minutes	7-23-98	7-24-98	7-24-98
Amendment	7-29-98	7-29-98	7-29-98

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C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>/C<sub>22</sub>H<sub>28</sub>O<sub>3</sub> (Estradiol/Norethindrone Acetate)  
272.39/340.47

**SUPPORTING DOCUMENTS:** None

**RELATED DOCUMENTS**

Chemistry Review #1, NDA 20-870, dated 7-14-98

**CONSULTS**

None

**REMARKS/COMMENTS**

A deficiency letter with respect to Chemistry Manufacturing and Control was sent on July 7, 1998 and the responses to the deficiencies are reviewed here. The 7-15-98 amendment contains response to the deficiencies recorded in Chemistry Review #1. The 7-23-98 correspondence is a Teleconference minutes from RPR regarding agreements reached on Crystal formation, stability issue, and imprinting on the backing. The amendment dated 7-29-98 was received as a facsimile with content uniformity data, updated storage conditions proposal, tighter total impurity specifications and status of the DMF

**CONCLUSION AND RECOMMENDATIONS**

With regard to chemistry, manufacturing and controls, the application is approvable pending the changes to be made and information to be submitted as noted here.

1. The Release Specifications for the drug product should be updated as follows.

A. Assay,

B.

The assay specifications for estradiol and NETA should be updated immediately as given above.

Methods including validation for \_\_\_\_\_ should be submitted in the form of a CBE supplement within 6 months of approval.

2. The Shelf Life Specifications for Total estradiol and NETA related impurities and release liner peel force should be updated immediately.

A. Total Estradiol Related Impurities %

B. Total NETA Related Impurities %

C. Release liner peel force- not more than \_\_\_\_\_ grams

The release liner peel force method should be provided.

3. \_\_\_\_\_ data on stability should be submitted as a Phase IV commitment by 9-1-98.

4. The storage conditions on the Pouch and Carton label should read as follows.

5. In the Packaging Insert the storage conditions should read as follows:

6. The sponsor should submit the revised stability commitment protocol immediately.

cc: NDA original  
HFD-580/A. K. Mitra, Ph.D  
HFD-580/M. J. Rhee, Ph.D  
HFD-580/J. Markow  
HFD-580/Div. File  
R/D Init. By

7/31/98

/S/

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Amit K. Mitra, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)  
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

**NDA # 20-870**      **Chemistry Review # 3**      **Review Date: 8-5-98**

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Hardcopy	8-3-98	8-3-98	8-3-98
Facsimile	8-4-98	8-4-98	8-4-98
Facsimile	8-5-98	8-5-98	8-5-98

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C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>/C<sub>22</sub>H<sub>28</sub>O<sub>3</sub> (Estradiol/Norethindrone Acetate)  
272.39/340.47

**SUPPORTING DOCUMENTS:** None

**RELATED DOCUMENTS**

Chemistry Review #2, NDA 20-870, dated 7-31-98

**CONSULTS**

None

**REMARKS/COMMENTS**

A deficiency letter based on the Chemistry Review #2 of the NDA was sent on 7-31-98 and the responses to the deficiencies are reviewed here.

**CONCLUSION AND RECOMMENDATIONS**

With regard to chemistry, manufacturing and controls, the application can now be approved. However, the sponsor should be reminded of the following Phase 4 commitments.

cc: NDA original  
HFD-580/A. K. Mitra, Ph.D  
HFD-580/M. J. Rhee, Ph.D  
HFD-580/J. Markow  
HFD-580/Div. File  
R/D Init. By . 8/5/98

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Amit K. Mitra, Ph.D