CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20130/S3

APPROVAL LETTER

NDA 20-130/S-003

Parke-Davis Pharmaceutical Research
Attention: Cheryl Beal Anderson, PharmD.
Manager, FDA Liason
Worldwide Regulatory Affiars
2800 Plymouth Road
Ann Arbor, MI 48105

MAY 7 1999

Dear Ms. Anderson:

Please refer to your supplemental new drug application dated December 23, 1997, received December 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrostep® (norethindrone acetate and ethinyl estradiol) tablets.

We acknowledge receipt of of your submission dated February 26, 1999. Your submission of February 26, 1999 constituted a complete response to our February 12, 1999 action letter.

This supplemental new drug application provides for labeling changes.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling with the revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

PRECAUTIONS section

In the paragraph related to Troglitazone, the word should be replaced by

This revision is a term of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-130/S-003." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 5/7/05

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-130
HFD-580/Div. Files
HFD-580/J.Mercier
HFD-580/Rarick/Mann/Allen/Parekh/Jarugula/Raheja/Jordan/Rhee/De
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JM/May 6, 1999
Initialed by: May 7, 1999/Rumble
final: May 7, 1999
filename: 20130S3A.WPD

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20130/S3

APPROVABLE LETTER

Attachment 1

NDA 20-130/S-003

FEB 12 1999

Parke-Davis Pharmaceutical Research
Attention: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Pitts:

Please refer to your supplemental new drug application dated December 23, 1997, received December 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrostep -21 (norethindrone acetate and ethinyl estradiol) Tablets and Estrostep-Fe (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate) Tablets.

We acknowledge receipt of your submission dated August 4, 1998.

This supplement proposes updating the **CLINICAL PHARMACOLOGY** section of the Prescribing and Patient Package Inserts with data obtained from biopharmaceutic studies.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

Prescribing Package Insert

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 2/12/99

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-130
HFD-580/Div. Files
HFD-580/VJarugula/AParekh/SAllen/SSlaughter
HFD-95/DDMS
DISTRICT OFFICE
HFD-580/CKish/12.30.98/n20130ae.s03
concurrence:VJarugula 1.6.99/AParekh 1.7.99/SAllen 1.6.99/SSlaughter 1.13.99/MMann 1.13.99

SUPPLEMENT APPROVABLE (S/AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20130/S3

MEDICAL REVIEW(S)

ORIGINAL

DEC 29 1998

Medical Officer Review of Draft Labeling

NDA:	20,130/S-003
Applicant:	Parke-Davis Pharmaceutical Research 2800 Plymouth Road, P.O. Box 1047 Ann Arbor, MI 48106-1047
Type of Submission:	Data in support of Phase IV commitment studies
Drug:	Estrostep® 21 and Estrostep® Fe
Generic Drug Name:	Norethindrone Acetate and Ethinyl Estradiol tablets (Estrostep® 21); Norethindrone Acetate, Ethinyl Estradiol and Ferrous Fumarate (Estrostep® Fe)
Indication for Use:	Contraception
Related Submissions:	IND IND
Original Submission date:	12/29/97
Date submission received by this reviewer:	12/7/98
Review completed:	12/28/98
Material reviewed:	Revised product labeling

Resume:

Estrostep® 21 is a combined oral contraceptive (OC) providing a constant dose of progestin and graduated doses of estrogen in a specific sequence over a 21-day period. Each packet of Estrostep® 21 contains, in order, five white triangular tablets containing 1 mg of norethindrone acetate (NA) and 20 μg ethinyl estradiol (EE); seven white square tablets containing 1 mg of NA and 30 μg EE; and nine white round tablets containing 1 mg of NA and 35 μg EE.

Estrostep® Fe is a combined oral contraceptive providing a constant dose of progestin and graduated doses of estrogen in the same sequence as that found in Estrostep ® 21 over a 21-day period. In addition, Estrostep ® Fe contains seven ferrous fumarate tablets, each of which is administered during the last seven days of a 28-day menstrual cycle. The ferrous fumarate tablets were added to Estrostep ® 21 not for any therapeutic purpose, but rather to "facilitate ease of drug administration" and enhance compliance with daily pill taking.

The original NDA for these products (NDA 20,130) was submitted to the Agency on December 27, 1990 and received a not approvable letter on August 27, 1992. Several amendments were made to the NDA,

with the result that the submission received formal approval by the Division of Reproductive and Urologic Drug Products on October 9, 1996. At the time the approvable letter was issued, the sponsor agreed to several Phase IV commitments as follows:

1. To conduct a multiple-dose biopharmaceutics study designed to address the deficiencies discussed with the Division of Biopharmaceutics prior to the original NDA approval. The protocol for this study was to be submitted within 30 days after approval of the NDA, and the study was to be completed within one year following the sponsor's receipt of the Agency's comments on the protocol. The study was to use the marketed tablets and was to incorporate dosing regimens of the product consistent with its labeling.
2. To update the CLINICAL PHARMACOLOGY section of the labeling using data from the above study and other relevant information upon completion of the study described in item #1.
3. To submit additional dissolution profiles for three production lots of each strength Estrostep® tablets using the new official USP method within the six months following issuance of the approval letter.

On December 29, 1997, the Agency received a submission containing the data and information from three studies which addressed the first two Phase IV commitments noted above. These studies included:

(1) a multiple-dose pharmacokinetic (PK) study,
(2) a food effect and relative bioavailability study, and
(3) a drug-drug interaction study.

Each of these studies was reviewed by Clinical Pharmacology and Biopharmaceutics in detail as described in their review. The majority of the findings from these studies were not thought be clinically significant; however, a 29% decrease in mean C_{max} of EE and a 27% increase in mean area-under-the-curve (AUC) values for NA were observed when Estrostep® was taken in the presence of food. Although the Biopharmaceutics reviewer noted that these changes were not likely to be clinically significant, the reviewing medical officer's opinion was sought in this regard.

Reviewer's comments:

Several pharmacokinetic studies conducted to examine the effect of other medications on plasma concentrations of synthetic steroids have demonstrated that certain drugs (such as Rifampin and some anticonvulsants) administered concomitantly with OCs are associated with a significant decrease in AUC for EE and synthetic progestins. This reduction in AUC for EE in OCs has been associated with break-through bleeding and reduced contraceptive efficacy[1]. In contrast to these drug products, clear correlations between a reduction in plasma levels or C_{max} of steroid hormones and decreased contraceptive efficacy has not been demonstrated. The degree of decrease in plasma levels of steroid hormones which would be associated with decreased clinical efficacy is not known[2].

Per discussions with the Biopharmaceutics review team, the parameter of most significance when evaluating the biopharmaceutical profile of a drug product taken daily and taken chronically (such as OCs) is the AUC, which reflects drug bioavailability, as compared to the Cmax or mean plasma concentration. From the food effect study performed, a comparison of the AUC values for EE and

[1] Back DJ and Orme ML. Pharmacokinetic Drug Interactions with Oral Contraceptives. *Clin Pharmacokinet.* 1990. 18(6)472-484.
[2] Neely JL, Abate M et al. The Effect of Doxycycline on Serum Levels of Ethinyl Estradiol, Norethindrone and Endogenous Progesterone. *Obstet Gynecol.* March, 1991. 77(3).

NA following a high-fat meal as compared to administration in a fasting state demonstrated a 5.7% and 27% increase in AUC values for EE and NA, respectively, following a high-fat meal. Thus, the 29% reduction noted in Cmax for EE in the presence of food is not thought to be of clinical significance based upon currently available knowledge. The increase in mean AUC of NA in the presence of food is also not thought to be of clinical significance.

Most importantly, there were no restrictions placed on food consumption relative to the timing of Estrostep administration in the clinical trials conducted under this NDA. Thus, evidence to support a reduction in contraceptive efficacy of Estrostep when consumed in the presence of food is lacking.

Findings from the biopharmaceutics studies described above resulted in changes in the following sections of the proposed labeling:

- "PRECAUTIONS-DRUG INTERACTIONS" subsection
- DOSAGE AND ADMINISTRATION section
- DETAILED PATIENT PACKAGE INSERT section.

The changes in these sections of the label focus on new statements regarding the drug interaction effects of other drugs *on oral contraceptives* as well as the effects of oral contraceptives *on other drugs*.

The Effects of Other Drugs on Oral Contraceptives

Specific drugs and drug classes noted to have interaction effects on oral contraceptives which are mentioned in the proposed labeling include Rifampin, Troglitazone, Atorvastatin, Acetominophen, ascorbic acid, antibiotics, and anticonvulsants.

The anticonvulsants Phenobarbital, Phenytoin and Carbamazepine and the antibiotic Rifampin when coadministered with OCs cause an induction of microsomal enzymes that results in a significant decrease in AUC for both EE and synthetic progestins such as LNG and norethisterone. The anticonvulsant Valproic Acid has no detectable effect on the pharmacokinetics of EE or LNG.

Clinical pharmacokinetic studies of the effects of antibiotics other than Rifampin on OCs have been unsuccessful in demonstrating a consistent effect of these drugs on plasma concentrations of synthetic steroids. The studies which have been conducted to date examining this issue consist primarily of retrospective, uncontrolled, individual case reports or of small studies demonstrating extensive inter-individual variability and inconsistent overall results. While previously conducted studies have not shown consistent interaction between antibiotics (other than Rifampin) and OCs, the large degree of inter-individual variability noted in study results implies that certain women may be at risk of an antibiotic-OC interaction that could affect contraceptive effectiveness. These women would have an unusually low EE bioavailability during OC administration that could result from extensive metabolism of EE in the gastrointestinal (GI) tract or a large enterohepatic recirculation of EE[3].

As part of its metabolism, EE is conjugated with both sulphate and glucuronic acid[2]. Studies have demonstrated that both acetaminophen and ascorbic acid are extensively sulphated in the gastrointestinal tract and thus compete with EE for this pathway. As a result, some studies have demonstrated that administration of either acetaminophen or ascorbic acid with EE has been associated with significant increases in AUC and/or plasma concentrations of EE.

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[3] Shenfield, GM. Oral Contraceptives: Are Drug Interactions of Clinical Significance? *Drug Safety.* 1993. 9(1):21-37.

In the case of ascorbic acid, studies of the interaction of this vitamin and EE have produced conflicting results. Women given a 1 gram dose of ascorbic acid followed shortly thereafter by a single dose of EE were noted to have a 60-70% increase in EE bioavailability compared to bioavailability when no ascorbic acid was administered[4]. In another study, women given a 1 gram per day dose of ascorbic acid concomitantly with an EE-containing OC were noted to have a 47% increase in plasma EE concentration above that seen when ascorbic acid was not administered[5]. These results conflict with those from a more recent study in which daily co-administration of 1 g of Vitamin C with an OC containing 30 μg of EE did not cause an increase in systemic availability of EE[6].

Troglitazone (Rezulin™) is an oral antihyperglycemic agent which lowers serum glucose by improving target cell response to insulin. In humans, the drug is metabolized to form a sulfate conjugate, a glucuronide conjugate and a quinone metabolite. A study conducted by Loi et al and provided as a reference in the current submission revealed that coadministration of Troglitazone and an oral contraceptive (Ortho-Novum 1/35) resulted in a decrease in the C_{max} and AUC values for EE by 32% and 29%, respectively. Mean norethindrone C_{max} and AUC values also decreased by 31% and 30%, respectively[7].

Atorvastatin (CI-981) is an investigational HMG-CoA reductase inhibitor which, in a clinical setting, might be taken by some individuals who are also taking oral contraceptives. The sponsor conducted an open-label, multiple-dose, drug-drug interaction study to determine the effect of multiple-dose Atorvastatin administration on the pharmacokinetics of norethindrone and ethinyl estradiol in healthy female volunteers. Results from the study demonstrated that coadministration of Atorvastatin with a combined oral contraceptive (Ortho-Novum 1/35) increased the AUC values for both ethinyl estradiol and norethindrone by approximately 20% and 30%, respectively[8]. These increases in AUC values would result in increased systemic exposure to ethinyl estradiol and norethindrone.

Reviewer's comments:

1. **The sponsor's proposed statements on the drug interaction effects of Rifampin and anticonvulsants are acceptable provided that the phrase(_ is replaced with**
2. **The sponsor's proposed statements on the drug interaction effects of antibiotics should be modified to state**

3. **The increases in AUC values for EE and NA noted with coadministration of Atorvastatin would result in increased systemic exposure to ethinyl estradiol and norethindrone acetate. AUC value**

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[4] Back DJ, Bates M, et al. Metabolism by gastrointestinal mucosa---clinical aspects. In Prescott & Nimmo (Eds) Drug Absorption., ADIS Press, Sydney. 1980. Pp.80-87.

[5] Back DJ, Breckenridge AM, et al. Interaction of ethinyloestradiol with ascorbic acid in man. *Br Med J.* May, 1981. 282:1516.

[6] Zamah NM, Humpel M, et al. Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception.* 1993 Oct. 48(4):377-391.

[7] Loi CM and Randinitis EJ. A study to determine the effects of Troglitazone (CI-991) on the pharmacokinetics of an oral contraceptive agent (Ortho-Novum 1/35) containing norethindrone acetate and ethinyl estradiol: Protocol 991-99, submitted to NDA 20-720 on January 31, 1997.

[8] Yang BB, Smithers JA et al. A study to determine the effects of Atorvastatin (CI-981) on the pharmacokinetics of an oral contraceptive agent (Ortho-Novum 1/35): Protocol 981-66, RR 644-00229, reissued July 10, 1996.

increases of this magnitude for both the ethinyl estradiol and progestin found in Estrostep® are not thought to be of clinical significance. Thus, the sponsor's proposed statements on the drug interaction effects of Atorvastatin are acceptable.

4. **As stated above, there is conflicting evidence regarding the effect of ascorbic acid administration on plasma concentrations and/or bioavailability of EE. The clinical significance of a statistically significant increase in bioavailable EE following coadministration with ascorbic acid has not been demonstrated. The sponsor's proposed statements on the drug interaction effects of ascorbic acid and Acetaminophen are acceptable.**
5. **The sponsor's proposed statements on the drug interaction effects of Troglitazone should state**

The Effects of Oral Contraceptives on Other Drugs

In vitro and preclinical animal studies have provided evidence that oral contraceptive steroids can have inhibitory effects on concurrently administered drugs. The inhibitory effects are thought to be due to a reduction of cytochrome P450 levels and enzymatic activity. The clearance of several drug products and other agents (including Theophylline, Prednisolone, caffeine and Cyclosporin) is reduced in women using contraceptive steroids. The clearance of other drugs (including Acetaminophen, Salicylic Acid, Morphine Temazepam and Clofibric Acid) is increased in contraceptive steroid users[1].

Reviewer's comments:

1. **The sponsor's proposed statements on the effects of oral contraceptives on other drugs should have the following italicized words added for completeness:**

Subsections of the Label related to "Dosage and Administration" and the "Patient Package Insert"

The sponsor proposes to delete text under the "Dosage and Administration" section of the physician label which states,

Reviewer's comments:

1. **Results from the Food Effect and Relative Bioavailability study demonstrated a 5.7% and 27% increase in AUC values for EE and NA, respectively, following a high-fat meal. As noted above, these findings were not thought to be of clinical significance based upon currently available knowledge. Thus, the sponsor's proposal to delete the text above from the "Dosage and Administration" section of the label for both the 21-day and the 28-day dosage regimens is acceptable.**

The only modifications noted in the "Detailed Patient Package Insert" occur in section 4 ("Drug Interactions") of the insert. The sponsor proposes to delete " from the list of drugs stated to interact with and reduce the effectiveness of OCs and to insert " into the list of these drugs.

In support of deletion of from the sections of the label and patient package insert noted above, the sponsor provided a reference by Gupta et al[9] which studied the effect of a combination OC on the metabolism of aspirin and phenylbutazone. The results from this study demonstrated that plasma levels, plasma half-life and AUC for aspirin were significantly lower after administration of the OC, while plasma levels of phenylbutazone were unchanged by administration of the OC.

Reviewer's comments:

1. **The sponsor's request to delete from the sections of the patient package insert and label described above appears to be supported by currently available literature.**
2. **The sponsor's request to add to the section of the patient package insert noted above is acceptable.**
3. **Section 4 of the patient package insert should reflect changes made in the "Drug-Drug Interactions" section of the label as follows:**

   - **Carbamazepine should be added to the list of drugs known to interact with (and possibly reduce the effectiveness of) OCs;**
   - **A statement should be added to this section of the package insert describing the effect of OCs *on other drugs*. Suggested wording would be: "Birth control pills may interact with certain drugs to make the other drugs more or less effective. Such drugs include Cyclosporine, Prednisolone, Theophylline, Temazepam and Acetaminophen.**

Conclusions

It is recommended that the proposed labeling changes be accepted pending incorporation of suggested comments as described above in this review.

/S/

Susan S. Allen, MD, MPH
Medical Officer, DRUDP

Concurrence:

/S/ , M.D. 12/29/98

Marianne Mann, MD
Deputy Director, DRUDP

cc: HFD 580/Division Director
NDA 20,130/Division File
S.Allen/M.Mann/L.Rarick

[9] Gupta KC, Joshi JV, et al. Effect of low estrogen combination oral contraceptive on metabolism of aspirin and phenylbutazone. *Int J Clin Pharm, Ther and Tox.* 1982. 20(11):511-513.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20130/S3

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ORIGINAL

OCT 2 1998

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-130/S003, IND , IND
Drug:	Estrostep® (Norethindrone acetate and ethinyl estradiol tablets)
Sponsor:	Parke-Davis
Date of Submission:	12/23/97, 8/4/98
Type of Submission:	Phase IV commitment
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

NDA 20-130 for Estrostep® was approved on 10/09/96 with a Phase IV commitment to do a multiple dose pharmacokinetic study and revise the labeling. Estrostep® was approved for use as an oral contraceptive in women with the following regimen: One Estrostep 1/20 tablet (1mg norethindrone acetate/20 μg ethinyl estradiol) daily for 5 days, one estrostep 1/30 tablet daily for the next 7 days, and one estrostep 1/35 tablet daily for the remaining 9 days. The tablet formulation differs only in ethinyl estradiol content.

In order to fulfill the Phase IV commitments, the sponsor included the multiple dose study report and the revised labeling incorporating the results of the multiple dose study in the current submission. The sponsor also submitted a food effect study and a drug interaction study, which were conducted under IND for hormone replacement therapy, to support other proposed changes in the labeling.

Multiple dose PK study: This study was also submitted to IND on 12/23/97 and the results of the study showed that:

- Steady-state accumulation of ethinyl estradiol (EE) was slightly greater than predicted from single dose pharmacokinetics. However, this slight accumulation is neither statistically nor clinically significant.

- Steady-state accumulation of norethindrone (NE) was significantly greater than predicted from single-dose pharmacokinetics. The observed accumulation of norethindrone was attributed to an increase in plasma steroid hormone binding globulin (SHBG) concentrations induced by ethinyl estradiol and this is in agreement with the available information on norethindrone.

- The pharmacokinetics of ethinyl estradiol following multiple dose administration were dose proportional in the range of doses administered (20, 30 and 35 μg).

- Mean steady-state plasma concentrations of norethindrone for the 1/20, 1/30, and 1/35 tablets strengths increase as ethinyl estradiol dose increases; this is due to the dose dependent increases in serum SHBG concentrations.

- The mean plasma free testosterone levels during the third cycle of multiple dose administration (cycle 4) were approximately 35% to 55% of the mean baseline value indicating that Estrostep has minimal androgenic activity.

Food effect and relative bioavailability study: This study was also submitted to IND [redacted] on 12/23/97 and the results of the study showed that:

- Administration of two 1/10 NA/EE tablets with a high fat meal decreased the rate but not the extent of EE absorption. The C_{max} of EE was decreased by 29%.

- The rate of absorption of NE was slightly decreased but the extent of absorption ($AUC_{0-\infty}$) of NE was increased by 27% in the presence of food probably because of the increased transit time in the gastrointestinal tract.

Drug-Drug interaction study:
This study was also submitted to IND [redacted] on 5/23/97 and the results of the study showed that:

- Plasma EE levels following single dose administration of a 1/10 NA/EE hydroalcoholic solution were consistently higher than those following adminstration of 10μg EE hydroalcoholic solution, resulting in 16% and 28% higher mean C_{max} and $AUC_{(0-\infty)}$, respectively. The levels of EE were higher than expected, considering the metabolic conversion of NE to EE.

- When norethindrone alone was administered, a small amount of norethindrone was metabolically converted to ethinyl estradiol.

- The pharmacokinetics of NE was not affected by the presence of EE following single dose adminstration of 1/10 NA/EE solution.

Reviewer Comments:

- It should be noted that the formulation used in the food effect study is slightly different from that of Estrostep. However, based on the comparative *in vitro* dissolution data and the similar pharmacokinetic data observed in a cross study comparison with a single dose 1/35 NA/EE arm in the multiple dose study, the results of food effect study can be applied to Estrostep.

- The 29% decrease in mean Cmax of EE and 27% increase in mean AUC of NE observed in the presence of food are not likely to be clinically significant. However, the reviewing medical officer's opinion should be considered in this regard.

- The higher plasma EE concentrations observed following the administration of 1/10 NA/EE hydroalcoholic solution than those after 10 μg EE alone are probably due to the metabolic conversion of NE to EE. However, plasma EE levels were higher than anticipated, considering the metabolic conversion of NE to EE. Several literature articles also reported that NA metabolically converts to EE. This observation is not likely to be of clinical significance because the safety and efficacy of the Estrostep (with a triphasic dosage regimen) was studied in phase III clinical trials.

- Following single dose administration, the pharmacokinetics of NE is not affected by the coadministration of EE. However, it is known that chronic administration of NA and EE together leads to accumulation of NE due to the induction of SHBG synthesis by EE.

Labeling changes: Sponsor updated the clinical pharmacology section of the labeling to incorporate the information obtained in the above studies. The updated version is included in attachment II. The following labeling comments should be conveyed to the sponsor.

Labeling Comments:

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed NDA 20130/s003 dated 12/23/97 and 8/4/98. The proposed labeling changes and the results of multiple dose study conducted as part of Phase IV commitment are acceptable provided the labeling comments 1 through 5 are addressed by the sponsor.

The sponsor should be reminded about the third Phase IV commitment regarding *in vitro* dissolution profiles that was mentioned in FDA's letter dated 10/9/96.

The proposed changes in the labeling regarding drug interactions should also be reviewed by the reviewing medical officer of HFD-580.

Please convey the Recommendation and labeling comments 1 through 5 to the sponsor as appropriate.

/S/ 10/2/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Team Leader, Ph.D. AP 10/2/98

FT initialed by Ameeta Parekh, Team Leader, Ph.D. /S/ 10/2/98

cc: NDA 20130/S003, HFD-580 (Bennette, Kish), HFD-870 (M.Chen, parekh, Jarugula), CDR (B.Murphy for Drug).

SUMMARY OF THE STUDIES

Synopses of the individual studies submitted to the supplement are included in Attachment I. A brief summary and analyses of the results submitted in these studies is given below.

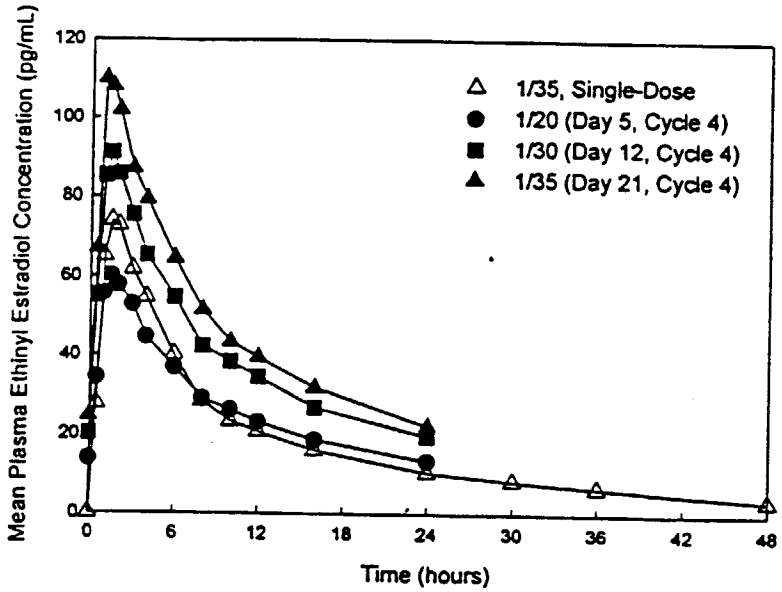
Multiple Dose Pharmacokinetic study (RR 744-00376):

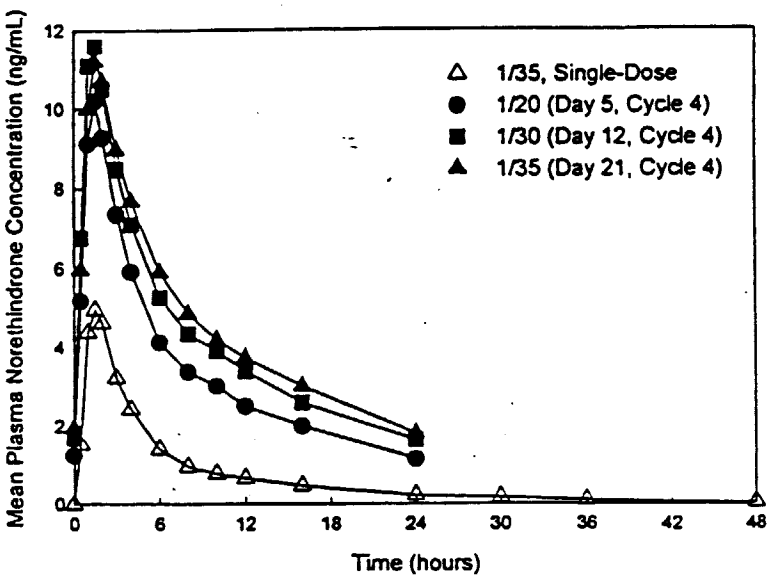
In an open-label, nonrandomized, single- and multiple dose study, the steady-state pharmacokinetics was investigated in 18 healthy female subjects. Who received the following treatments:

Cycle	Cycle Day(s)	Dose and Formulation	Time of dosing
1	1	1 Estrostep 1/35 tablet	AM
2,3, and 4	1-5	1 Estrostep 1/20 tablet	AM
	6-12	1 Estrostep 1/30 tablet	AM
	13-21	1 Estrostep 1/35 tablet	AM

Plasma samples collected for 24 or 48 hours after each treatment were assayed for ethinyl estradiol (EE) and norethindrone (NE) concentration by a validated__ method.

The mean plasma concentrations of EE and NE following single and multiple dose administration are illustrated below:





The mean (SD) pharmacokinetic parameters derived from plasma concentrations of EE and NE are listed in the following table:

Parameter	Single Dose 1/35 (N=19)	Steady-state 1/20 (N=17)	1/30 (N=17)	1/35 (N=16)
Ethinyl Estradiol				
C_{max} (pg/ml)	77.7 (21.8)	61.0 (16.8)	92.4 (26.9)	113 (44)
T_{max} (h)	1.5 (0.4)	1.5 (0.3)	1.5 (0.3)	1.4 (0.3)
C_{24} (pg/ml)	10.5 (3.5)	13.5 (5.7)	19.8 (9.3)	22.4 (9.1)
$AUC_{(0-24)}$ (pg.hr/ml)	666 (194)	661 (190)	973 (293)	1149 (372)
$AUC_{(0-\infty)}$ (pg.hr/ml)	937 (272)	ND	ND	ND
$T_{1/2}$ (hr)	16.3 (4.8)	ND	ND	19.3 (6.9)
Norethindrone				
C_{max} (pg/ml)	5.45 (2.61)	10.8 (3.9)	12.7 (4.1)	12.7 (4.1)
T_{max} (h)	1.7 (0.8)	1.7 (0.8)	1.6 (0.8)	2.1 (1.4)
C_{24} (pg/ml)	0.22 (0.18)	1.16 (0.59)	1.64 (0.83)	1.81 (0.74)
$AUC_{(0-24)}$ (pg.hr/ml)	27.6 (15.1)	81.1 (28.5)	102 (32)	109 (32)
$AUC_{(0-\infty)}$ (pg.hr/ml)	31.7 (17.9)	ND	ND	ND
$T_{1/2}$ (hr)	9.98 (3.52)	ND	ND	12.8 (3.6)

Based on ratios (steady-state/single dose) of C_{max}, C_{24}, and $AUC_{(0-24)}$ values, steady-state accumulation of EE ranged from 1.45 to 2.15 which is more than the accumulation factor (1.37) predicted from single-dose.

Steady state accumulation of NE ranged from 2.33 to 8.18 which is significantly more than the predicted accumulation factor (1.12) from single dose pharmacokinetics.

The mean serum sexual hormone binding globulin (SHBG) concentrations during the third cycle of Estrostep multiple administration were approximately 2 to 3 times higher than baseline values.

The mean plasma free testosterone levels during the third cycle of multiple dose administration (cycle 4) were approximately 35% to 55% of the mean baseline value indicating that Estrostep has minimal androgenic activity.

Mean steady-state C_{max} and $AUC_{(0-24)}$ values indicate that the pharmacokinetics of EE are dose proportional over 20 to 35 µg dose range.

Reviewer Comments:

The steady state accumulation of NE is significantly greater than predicted from single-dose pharmacokinetics due to the 2- to 3-fold increase in serum SHBG concentrations during treatment with Estrostep.

The pharmacokinetics of EE is dose proportional following multiple administration of Estrostep in the dose range of 20 to 35 µg.

Mean steady-state plasma concentrations of NE increase as EE dose increases because of the dose dependent increases in serum SHBG concentrations.

Single-dose Food-effect and relative bioavailability study (RR 744-00296):

This study determined the effect of food on NE and EE absorption from NA/EE tablets, and the bioavailability relative to an oral solution. This open-label, single-dose, randomized, 3-way crossover study enrolled 18 healthy postmenopausal women who received the following three treatments with a one week washout period after each treatment.

Trt 1: 2 market-image NA/EE 1/10 tablets administered while fasting,
Trt 2: 2 market-image NA/EE 1/10 tablets given 15 minutes after high fat breakfast
Trt 3: 2 mg NA/20 µg EE hydroalcoholic solution administered while fasting

The formulation (WL 57184-68) used in this study was the proposed market image 1mg NA/10 µg EE FemHRT tablet formulation which is being developed under IND
The composition of FemHRT and Estrostep tablet formulations is included in attachment II. The composition of two formulations appears to be similar except for the amount of EE, which ranges from 20 to 35 µg in Estrostep formulation. However, the following minor differences exist:

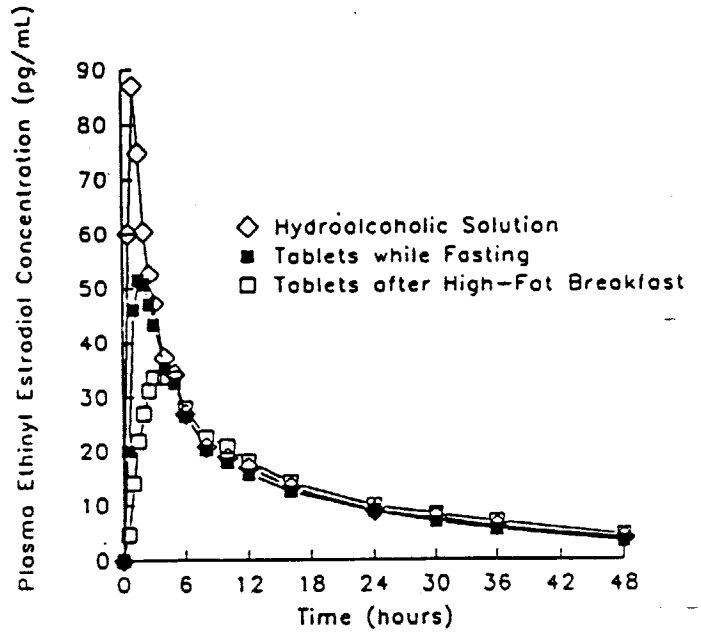
- FemHRT tablets were manufactured with 5% overage for EE. The current approved Estrostep formulation has no EE overage.

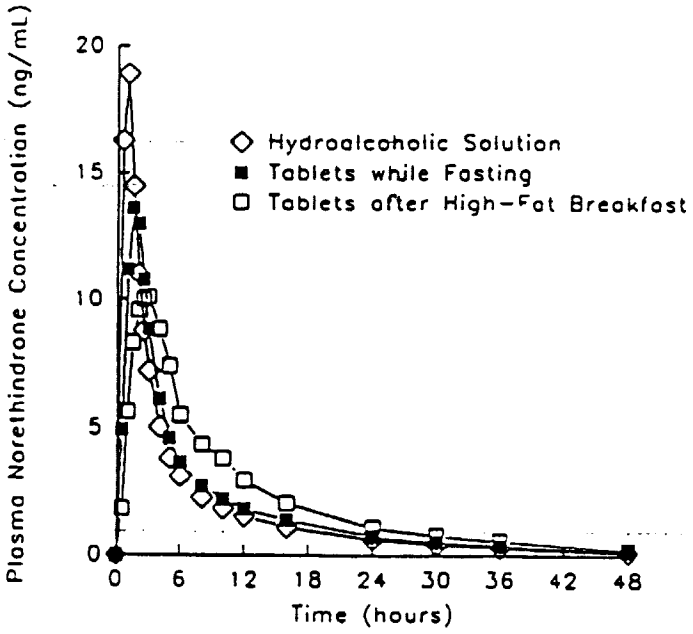
- There are also some manufacturing differences between FemHRT and Estrostep. The solids processor, a closed system for material handling and processing, is used in the

FemHRT process. The Order of excipient addition and the drying processes are different.

The sponsor submitted *in vitro* dissolution profiles for the two formulations (see attachment I) and the dissolution of the two formulations is found to be similar.

The mean plasma concentrations of EE and NE from this study are illustrated in the figure below:





The mean pharmacokinetic parameters of EE and NE are listed below:

Parameter	Trt A	Trt B	Trt C	%Difference B/A	%Difference A/C
Ethinyl Estradiol[a]					
C_{max}[b] (pg/ml)	51.4	36.5	84.7	-29.0	-39.3
T_{max} (hr)	1.58	3.69	1.06	134	49.1
$AUC_{(0-t)}$[b] (pg.h/ml)	595	603	692	1.34	-14.0
$AUC_{(0-\infty)}$[b] (pg.h/ml)	686	725	798	5.69	-14.0
$T_{1/2}$ (h)	16.7	18.4	17.6	10.2	-5.11
Norethindrone[a]					
C_{max}[b] (ng/ml)	13.3	11.7	18.2	-12.0	-26.9
T_{max} (h)	1.61	2.47	0.86	53.4	87.2
$AUC_{(0-t)}$[b] (pg.h/ml)	77.8	98.5	74.6	26.6	4.29
$AUC_{(0-\infty)}$[b] (pg.h/ml)	80.6	102	77.0	26.6	4.68
$T_{1/2}$ (h)	10.4	10.3	10.1	-0.96	2.97

a: Dose= 2mg NA/20 µg EE
b: parameters calculated using log-transformed data.
Trt A: Two tablets of 1/10 NA/EE while fasting
Trt B: Two tablets of 1/10 NA/EE following a high-fat meal
Trt C: 2 mgNA/20 µg EE hydroalcoholic solution orally

Rate of EE absorption from NA/EE 1/10 tablets was slower when administered with high-fat breakfast than while fasting. In the presence of food, the Tmax was delayed from 1.58 h to 3.69 h and C_{max} was decreased by 29%. However, the extent of absorption was not affected.

Rate of NA absorption from NA/EE 1/10 tablets was also decreased in the presence of a high-fat meal, but the decrease was not as large as that for EE. For NA, 12% decrease in C_{max} and a delay in T_{max} from 1.6 h to 2.5 h.

The relative bioavailability of EE and NE from the tablets compared to oral solution was 86% and 100%, respectively.

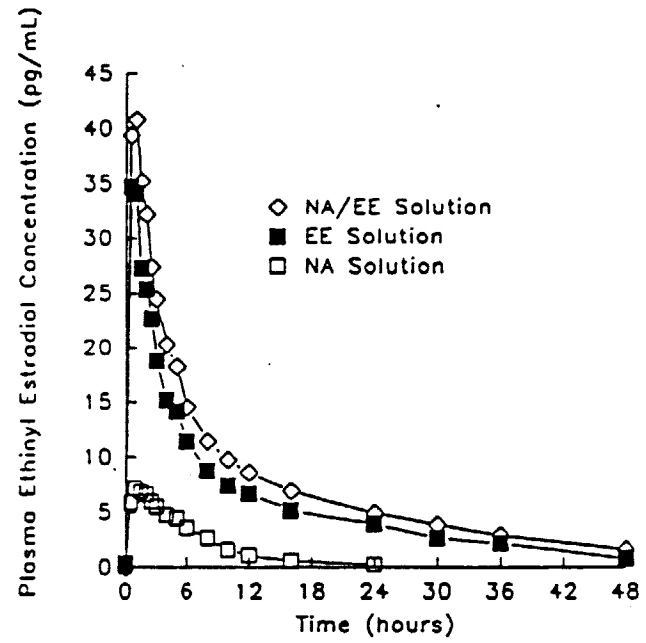
Reviewer Comment:
Although a food effect study with the approved formulation with the highest dose is desirable, the formulation used in the sponsor's study is similar to the approved Estrostep formulation and the *in vitro* dissolution of the two formulations is similar. Upon cross study comparison, the pharmacokinetics of EE was found to be similar following single dose 1/35 NA/EE administration in the multiple dose study and 2x1/10 NA/EE administration in food effect study. Therefore, the food effect results obtained in the current study can be applicable to the Estrostep formulation.

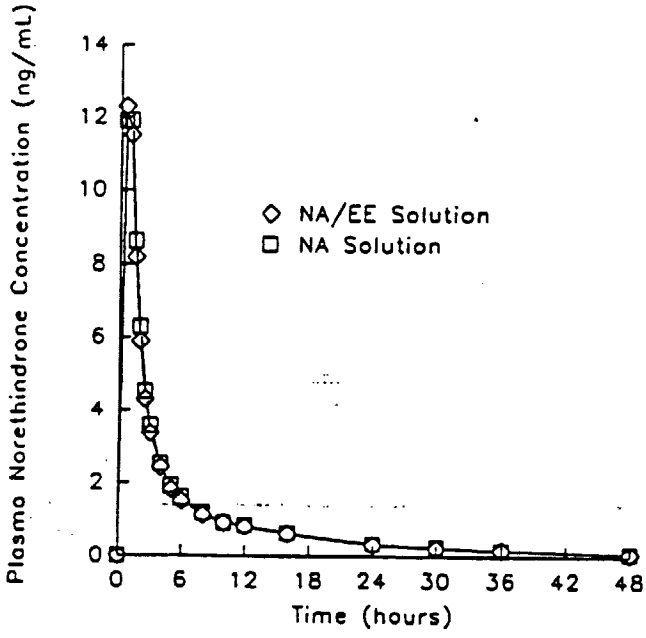
Single dose drug interaction study (RR 744-00300):

This is an open-label, single-dose, randomized, 3-way crossover study in 18 healthy postmenopausal women who received the following three treatments on three occasions separated by one week washout period.

Treatment 1: 1mg NA/10 μg EE hydroalcoholic solution
Treatment 2: 1 mg NA hydroalcoholic solution
Treatment 3: 10 μg EE hydroalcoholic solution

The mean plasma concentrations of EE and NE measured in this study are illustrated in the figure below:





The mean pharmacokinetic parameters for EE and NA for this study are listed below:

Parameter	10μg EE (N=17)	1/10 NA/EE (N=17)	1mg NA (N=16)	%Difference
Ethinyl Estradiol				
C_{max}[a] (pg/ml)	35.5	41.3	7.03	16.3
T_{max} (h)	0.84	0.79	1.05	-5.95
$AUC_{(0-t)}$[a] (pg.h/ml)	262	351	41.7	34.0
$AUC_{(0-\infty)}$[a] (pg.h/ml)	327	420	ND	28.4
$T_{1/2}$ (h)	18.0	17.7	ND	-1.67
CL/F (ml/min)	535	409	ND	-23.6
Norethindrone				
C_{max}[a] (ng/ml)		12.3	12.3	0.00
T_{max} (h)		0.74	0.70	-5.41
$AUC_{(0-t)}$[a] (ng.h/ml)		42.5	42.5	0.00
$AUC_{(0-\infty)}$[a] (ng.h/ml)		44.7	44.3	-0.89
$T_{1/2}$ (h)		10.7	10.6	-0.94
CL/F (ml/min)		357	356	-0.28

a parameters calculated using log-transformed data

Plasma EE concentrations following single-dose administration of a 1/10 NA/EE hydroalcoholic solution were consistently higher than those following administration of 10 μg EE solution resulting in 16% higher mean C_{max} and 28% higher $AUC_{(0-\infty)}$ values.

Measurable concentrations of EE were observed following the administration 1 mg NA hydroalcoholic solution. The presence of additional EE in the dosing solutions, the assay interference and conversion during the sample preparation have been ruled out. Therefore the appearance of EE plasma levels following the administration NA solution indicates metabolic conversion of NA to EE.

Comments:

The higher plasma EE concentrations observed following the administration of 1/10 NA/EE hydroalcoholic solution than those after 10 μg EE alone are probably due to the metabolic conversion of NE to EE. Several literature articles also reported that NA metabolically converts to EE. This observation is not likely to be of clinical significance because the safety and efficacy of the Estrostep (with a triphasic dosage regimen) was studied in phase III clinical trials.

Following single dose administration, the pharmacokinetics of NE is not affected by the coadministration of EE. However, it is known that chronic administration of NA and EE together leads to accumulation of NE due to the induction of SHBG synthesis by EE.

ATTACHMENT I
(Synopses of individual studies and formulation information)

Date of Report: March 12, 1997

Name of Company: 7	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

Title of the Study: A SINGLE-DOSE STUDY IN HEALTHY POSTMENOPAUSAL WOMEN COMPARING THE PHARMACOKINETICS OF NORETHINDRONE ACETATE/ETHINYL ESTRADIOL (NA/EE) ADMINISTERED ALONE AND IN COMBINATION (PROTOCOL 376-396)

Investigators:

Study Center(s): Parke-Davis Community Research Clinic, Ann Arbor, Michigan USA

Publication (reference): None

Studied Period (years): 09/06/95 to 09/26/95 | **Clinical Phase:** 1

Objective(s): Determine whether a pharmacokinetic interaction between norethindrone acetate and ethinyl estradiol occurs at doses used for hormone replacement therapy (1 mg and 10 µg, respectively)

Methodology: An open-label, single-dose, randomized, 3-way crossover study

Number of Subjects (total and for each treatment): Planned enrollment was 18 subjects.

Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers

Test Treatment, Dose and Mode of Administration, Batch Number: 1-mg NA/10-µg EE hydroalcoholic solution (20 mL), made from bulk drug [Parke-Davis Lots M09755 (NA) and M09804 (EE)], administered orally with an additional 220 mL of water

Duration of Treatment: Single oral doses

Reference Treatment, Dose and Mode of Administration, Batch Number: 1-mg NA hydroalcoholic solution (20 mL), made from bulk drug (Parke-Davis Lot M09755), administered orally with an additional 220 mL of water

Reference Treatment, Dose and Mode of Administration, Batch Number: 10-µg EE hydroalcoholic solution (20 mL), made from bulk drug (Parke-Davis Lot M09804), administered orally with an additional 220 mL of water

Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a[ ] method validated from 2 pg/mL, the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from 0.05 ng/mL, the lower limit of quantitation, to 25 ng/mL for norethindrone.

Criteria for Evaluation: Subjects completing all treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.

Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters and descriptive statistics (difference between least-squares treatment mean values and associated 95% confidence intervals) were inspected for trends likely to be of clinical relevance. Analysis of variance of pharmacokinetic parameters was used for calculation of confidence intervals using a model incorporating sequence, subject within sequence, period, and treatment effects.

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition: The 17 women who completed at least one treatment in this study had a mean (range) age of 58 (50-68) years, mean (range) weight of 68.4 (50.4-94.0) kg, and mean (range) height of 163.5 (158.0-174.0) cm.

Clinical: Norethindrone acetate and ethinyl estradiol administered alone and together were well-tolerated by healthy subjects.

Pharmacokinetics: Ethinyl estradiol and norethindrone parameter values are summarized in the following tables:

Parameter	Ethinyl Estradiol Least-Squares Mean Value			Difference[b] (%)	95% Confidence Interval[b]
	10-µg EE Solution (N = 17)	1/10 NA/EE Solution (N = 17)	1-mg NA Solution (N = 16)		
Cmax[a] (pg/mL)	35.5	41.3	7.03	16.3	-0.2 to 33.6
tmax (hr)	0.84	0.79	1.05	-5.95	-42.8 to 30.5
AUC(0-tldc)[a] (pg·hr/mL)	262	351	41.7	34.0	8.1 to 65.2
AUC(0-∞)[a] (pg·hr/mL)	327	420	ND	28.4	16.6 to 40.1
CL/F (mL/min)	535	409	ND	-23.6	-33.1 to -14.0
λz (1/hr)	0.0432	0.0411	ND	-4.86	-17.4 to 7.7
t½ (hr)	18.0	17.7	ND	-1.67	-14.2 to 10.9

ND = Not determined.

[a] Parameters calculated using log-transformed data

[b] Comparison of 1/10 NA/EE solution and 10-µg EE solution

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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Parameter	Norethindrone Least-Squares Mean Value		Difference (%)	95% Confidence Interval
	1-mg NA Solution (N = 16)	1/10 NA/EE Solution (N = 17)		
Cmax[a] (ng/mL)	12.3	12.3	0.00	-8.3 to 10.1
tmax (hr)	0.74	0.70	-5.41	-32.4 to 21.1
AUC(0-tldc)[a] (ng·hr/mL)	42.5	42.5	0.00	-4.9 to 4.7
AUC(0-∞)[a] (ng·hr/mL)	44.7	44.3	-0.895	-6.6 to 4.6
CL/F (mL/min)	357	356	-0.280	-7.2 to 6.6
λz (1/hr)	0.0698	0.0676	-3.15	-12.6 to 6.3
t½ (hr)	10.7	10.6	-0.935	-14.2 to 12.3

[a] Parameters calculated using log-transformed data

Plasma ethinyl estradiol concentrations following single-dose administration of a 1/10 NA/EE hydroalcoholic solution were consistently higher than those following administration of a 10-µg EE solution, whereas no differences in plasma norethindrone concentrations were observed. Measurable plasma concentrations of ethinyl estradiol were obtained following administration of a 1-mg NA solution (see figure below). The most likely explanation for higher ethinyl estradiol concentrations in the 1/10 NA/EE treatment group, given the appearance of ethinyl estradiol after administration of the 1-mg NA solution, was metabolic conversion of norethindrone to ethinyl estradiol. Alternative explanations for both observations, such as the presence of additional ethinyl estradiol in the dosing solutions and assay interference, were ruled out. Inhibition of ethinyl estradiol metabolism by norethindrone could have contributed to the higher ethinyl estradiol concentrations in the 1/10 NA/EE treatment group, but there is little support for such an interaction. Thus, the results support conversion of norethindrone to ethinyl estradiol to a small extent, with 1 mg norethindrone acetate producing plasma ethinyl estradiol concentrations equivalent to those expected following a 2.8-µg oral ethinyl estradiol dose.

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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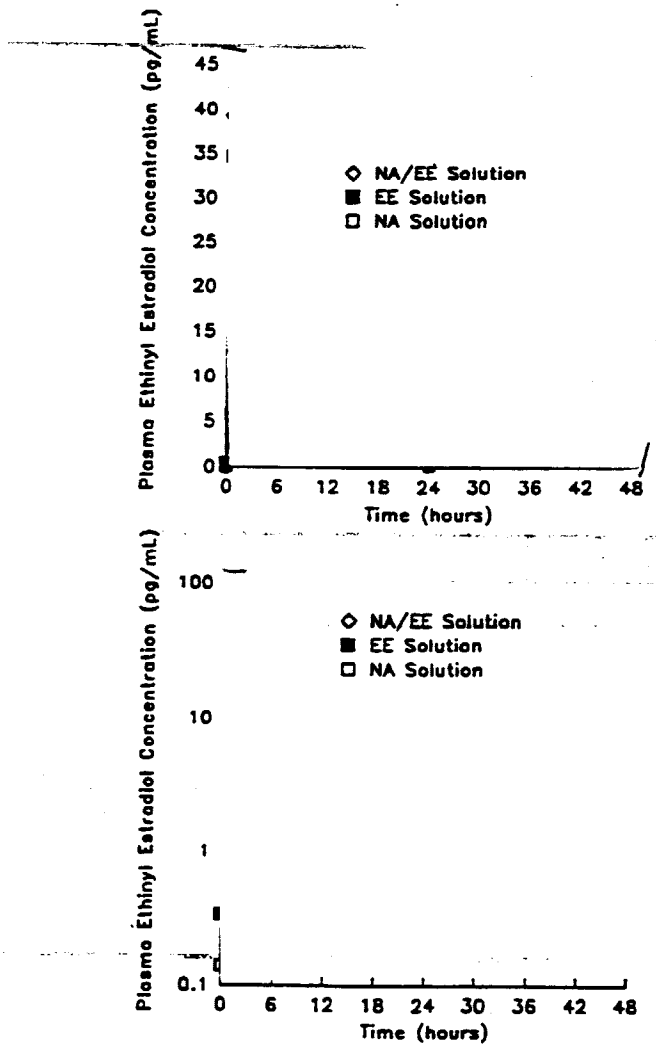

Conclusions: A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. No other pharmacokinetic interactions between norethindrone acetate and ethinyl estradiol are evident.

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

Title of the Study: A SINGLE-DOSE PHARMACOKINETIC STUDY IN HEALTHY POSTMENOPAUSAL WOMEN TO DETERMINE THE EFFECT OF FOOD ON MARKET-IMAGE NA/EE 1/10 (1 mg NORETHINDRONE ACETATE/10 µg ETHINYL ESTRADIOL) TABLETS AND TO DETERMINE THE BIOAVAILABILITY OF THE TABLETS RELATIVE TO AN ORAL SOLUTION (PROTOCOL 376-395)

Investigators:

Study Center(s):

Publication (reference): None

Studied Period (years): 12/08/95 to 12/24/95 **Clinical Phase:** 1

Objective(s): Determine the effect of administering market-image norethindrone acetate/ethinyl estradiol (NA/EE) 1/10 tablets with a high-fat breakfast on norethindrone and EE pharmacokinetics and determine the bioavailability of NA/EE 1/10 market-image tablets relative to an oral solution containing NA/EE

Methodology: An open-label, single-dose, randomized, 3-way crossover study

Number of Subjects (total and for each treatment): Planned enrollment was 18 subjects.

Diagnosis and Criteria for Inclusion: Healthy postmenopausal female volunteers

Test Treatment, Dose and Mode of Administration, Batch Number:

2 × market-image NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-68, Lot CX 0700695), administered orally with 8 fl oz of water

2 × market-image NA/EE 1/10 tablets (Parke-Davis Formulation WL 57184-68, Lot CX 0700695), administered orally with 4 fl oz of milk provided with a high-fat breakfast

Duration of Treatment: Single oral doses

Reference Treatment, Dose and Mode of Administration, Batch Number: 2 mg NA/20 µg EE hydroalcoholic solution (40 mL), made from bulk drug [Parke-Davis Lots M09755 (NA) and M09804 (EE)], administered orally with an additional 200 mL of water

Pharmacokinetic Sampling and Analysis: Plasma samples collected serially for 48 hours postdose were assayed for ethinyl estradiol and norethindrone by a method validated from 2 pg/mL, the lower limit of quantitation, to 1000 pg/mL for ethinyl estradiol and from 0.05 ng/mL, the lower limit of quantitation, to 25 ng/mL for norethindrone.

Criteria for Evaluation: Subjects completing all treatments and providing adequate concentration-time data were included in pharmacokinetic analysis. All subjects were included in safety analysis.

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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Pharmacokinetic and Statistical Methods: Noncompartmental pharmacokinetic parameters were calculated from observed plasma concentrations. Pharmacokinetic parameters and descriptive statistics (difference between least-squares treatment mean values and the associated 95% confidence intervals) were inspected for trends likely to be of clinical relevance. Analysis of variance of pharmacokinetic parameters was used for calculation of confidence intervals using a model incorporating sequence, subject within sequence, period, and treatment effects.

SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition: The 18 healthy postmenopausal women who completed this study had a mean (range) age of 59 (51-70) years, mean (range) weight of 69.6 (52.6-100.3) kg, and mean (range) height of 162.2 (148.5-172.7) cm.

Clinical: Overall, single, oral doses of 2 mg NA/20 µg EE were well-tolerated by healthy postmenopausal volunteers.

Pharmacokinetics: The effect of food on ethinyl estradiol and norethindrone pharmacokinetics is summarized in the following table:

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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Pharmacokinetics: (continued)

Parameter	Least-Squares Mean Value[a] Tablets While Fasting (N = 18)	Tablets After High-Fat Meal (N = 18)	Difference (%)	95% Confidence Interval
Ethinyl Estradiol				
Cmax[b] (pg/mL)	51.4	36.5	-29.0	-35.8 to -21.2
tmax (hr)	1.58	3.69	134	98.4 to 169
AUC(0-tldc)[b] (pg·hr/mL)	595	603	1.34	-3.0 to 5.7
AUC(0-∞)[b] (pg·hr/mL)	686	725	5.69	1.5 to 10.0
CL/F (mL/min)	506	474	-6.32	-10.6 to -2.1
λz (1/hr)	0.0441	0.0406	-7.94	-13.6 to -2.3
t½ (hr)	16.7	18.4	10.2	3.2 to 17.1
Norethindrone				
Cmax[b] (ng/mL)	13.3	11.7	-12.0	-21.9 to -1.0
tmax (hr)	1.61	2.47	53.4	21.2 to 85.7
AUC(0-tldc)[b] (ng·hr/mL)	77.8	98.5	26.6	15.9 to 38.1
AUC(0-∞)[b] (ng·hr/mL)	80.6	102	26.6	16.3 to 38.4
CL/F (mL/min)	402	309	-23.1	-36.1 to -10.1
λz (1/hr)	0.0710	0.0722	1.69	-3.2 to 6.6
t½ (hr)	10.4	10.3	-0.96	-4.8 to 2.9

[a] Dose = 2 mg NA/20 µg EE.
[b] Parameters calculated using log-transformed data.

Rate of ethinyl estradiol and norethindrone absorption from NA/EE 1/10 tablets administered with a high-fat breakfast was slower than the absorption rate when tablets were administered while fasting, based on comparisons of least-squares treatment mean Cmax and tmax values. Extent of ethinyl estradiol absorption, represented by least-squares mean AUC(0-∞) values, was essentially unaffected by administration with food, whereas extent of norethindrone absorption increased when NA/EE tablets were administered with food.

The bioavailability of ethinyl estradiol and norethindrone from NA/EE 1/10 tablets relative to that from a solution is summarized in the following table:

Name of Company:	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part of the Dossier	
Name of Active Ingredients: **Norethindrone Acetate and Ethinyl Estradiol**	Volume: Page:	

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Pharmacokinetics: (continued)

Parameter	Least-Squares Mean Value[a] Hydroalcoholic Solution (N=18)	Tablets While Fasting (N=18)	Difference (%)	95% Confidence Interval
Ethinyl Estradiol				
Cmax[b] (pg/mL)	84.7	51.4	-39.3	-45.3 to -32.8
tmax (hr)	1.06	1.58	49.1	-3.4 to 102
AUC(0-tldc)[b] (pg·hr/mL)	692	595	-14.0	-17.6 to -10.3
AUC(0-∞)[b] (pg·hr/mL)	798	686	-14.0	-17.4 to -10.5
CL/F (mL/min)	432	506	17.1	12.2 to 22.1
λz (1/hr)	0.0419	0.0441	5.25	-0.7 to 11.2
t½ (hr)	17.6	16.7	-5.11	-11.7 to 1.5
Norethindrone				
Cmax[b] (ng/mL)	18.2	13.3	-26.9	-35.2 to -18.0
tmax (hr)	0.86	1.61	87.2	26.7 to 147
AUC(0-tldc)[b] (ng·hr/mL)	74.6	77.8	4.29	-4.4 to 13.9
AUC(0-∞)[b] (ng·hr/mL)	77.0	80.6	4.68	-4.0 to 14.3
CL/F (mL/min)	430	402	-6.51	-18.7 to 5.6
λz (1/hr)	0.0739	0.0710	-3.92	-8.7 to 0.8
t½ (hr)	10.1	10.4	2.97	-1.0 to 6.9

[a] Dose = 2 mg NA/20 µg EE.
[b] Parameters calculated using log-transformed data.

Ethinyl estradiol and norethindrone were absorbed more slowly from NA/EE 1/10 tablets than from solution, based on a comparison of least-squares treatment mean Cmax and tmax values. Extent of ethinyl estradiol and norethindrone absorption from tablets was similar to that from solution.

Conclusions: Administration of NA/EE 1/10 tablets with a high-fat meal decreases rate but not extent of norethindrone and ethinyl estradiol absorption. NA/EE tablets can therefore be taken without regard to meals. Rate of ethinyl estradiol and norethindrone absorption is slower from NA/EE 1/10 tablets than from solution. The extent of ethinyl estradiol and norethindrone absorption from NA/EE 1/10 tablets is similar to that from NA/EE administered as a solution.

FemHRT Formulation From September 19, 1995 IND Submission

Formulation No.:	68
Label Claim (NA/EE):	1.0 mg/10.0 µg
	Amount Per Tablet
Norethindrone Acetate	mg
Ethinyl Estradiol	µg[a]
Lactose Monohydrate	mg
Starch	mg
Microcrystalline Cellulose	mg
Calcium Stearate	mg
Alcohol SD 3A Anhydrous[b]	µL
Purified Water USP[c]	µL
Tablet Weight	mg

[a] Includes 5% excess to account for manufacturing losses.
[b] Used as solvent in manufacture of the product and removed during drying.
[c] Used to aid removal of alcohol and removed during drying.

Estrostep Tablets Formulations From December 10, 1997 Annual Report

Ingredient	1/20 Tablets	1/30 Tablets	1/35 Tablets
	Amount Per Tab	Amount Per Tab	Amount Per Tab
Ethinyl Estradiol, USP	µg	µg	µg
Norethindrone Acetate, USP	ng	ng	ng
Modified Lactose Monohydrate, NF	mg	mg	mg
Alcohol SD 3A Anhydrous	ng[a]	ng[a]	ng[a]
Starch, Corn, NF	mg	mg	mg
Microcrystalline Cellulose, NF	mg	mg	mg
Calcium Stearate, NF Powder	mg	mg	mg
	mg	mg	mg

[a] Removed during process, final product may contain trace amounts.

ESTROSTEP Dissolution Profile Study - EE

Lot	Conc.	0	Time in Minutes				
			15	30	45	60	75
07806F	1/20	0					
074N6F	1/20	0					
075N6F	1/20	0					
Ave.	1/20	0					
067N6F	1/35	0					
068N6F	1/35	0					
069N6F	1/35	0					
Ave.	1/35	0					
071N6F	1/30	0					
072N6F	1/30	0					
073N6F	1/30	0					
Ave.	1/30	0					

ESTROSTEP Dissolution Profile Study - NA

Lot	Conc.	0	Time in Minutes				
			15	30	45	60	75
07806F	1/20	0					
074N6F	1/20	0					
075N6F	1/20	0					
Ave.	1/20	0					
067N6F	1/35	0					
068N6F	1/35	0					
069N6F	1/35	0					
Ave.	1/35	0					
071N6F	1/30	0					
072N6F	1/30	0					
073N6F	1/30	0					
Ave.	1/30	0					

Dissolution Profile of FemHRT LotCX-0700695 (04832) at the time of manufacture (Dissolution Media: pH 5/0.15% SLS).

	Norethindrone Acetate				Ethinyl Estradiol			
	Percent of L.C. Dissolved at				Percent of L.C. Dissolved at			
Sample No.	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	95	98	99	99	100	100	100	100
Range								

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20130/S3

ADMINISTRATIVE DOCUMENTS

12 1

MAR - 4 1999

CSO REVIEW OF DRAFT LABELING

NDA 20-130/S-003 Estrostep (norethindrone acetate and ethinyl estradiol) Tablets

Original Submission Date: December 23, 1997
Approvable letter Date: February 12, 1999
Labeling Amendment Date: February 26, 1999

MATERIAL REVIEWED

Physician's Insert (PI), Patient Brief and Detailed Package Inserts.

Background:

In the approval letter for the NDA dated October 9, 1996, the sponsor was requested to update their **CLINICAL PHARMACOLOGY** section of the Prescribing Package Insert upon completion of a multiple dose biopharmaceutics study. The sponsor completed the biopharmaceutics study and submitted the results along with revisions to their approved labeling to reflect the new information. The Division reviewed that submission and issued an approvable letter requesting further revisions (see attachment).

The sponsor has submitted draft labeling in response to the approvable letter. Changes to the requested revisions are delineated below:

Prescribing Information

[

Redacted 

pages of trade

secret and/or

confidential

commercial

information

Detailed Patient Package Insert

No other changes have been made to this label.

/S/

Christina Kish

4/9/99

cc:
Orig. NDA
HFD-580
HFD-580/SAllen/MMann/VJarugula/AParekh
HFD-580/CKish/3.4.99/n20301rv.2

ORIGINAL

DEC 29 1998

CSO REVIEW OF DRAFT LABELING

NDA 20-130/S-003 eSTROSTEP (norethindrone acetate and ethinyl estradiol) Tablets

Submission Date: December 23, 1997

MATERIAL REVIEWED

Physician's Insert (PI), Patient Brief and Detailed Package Inserts.

Background:
In the approval letter for the NDA dated October 9, 1996, the sponsor was requested to update their **CLINICAL PHARMACOLOGY** section of the Prescribing Package Insert upon completion of a multiple dose biopharmaceutics study.

The sponsor has completed the biopharmacuetics study and has submitted the results along with revisions to their approved labeling to reflect the new information.

The Division of Biopharmaceutics has reviewed the **CLINICAL PHARMACOLOGY** section, therefore the CSO review will be confined to changes which appear in sections other than the **CLINICAL PHARMACOLOGY** section.

Prescribing Information

Pregs while taking TCs ok

No other changes to section other than the CLINICAL PHARMACOLOGY section have been made to this label.

/S/

Christina Kish 12/29/98

cc:
Orig. NDA
HFD-580
HFD-580/CKish/12.4.98/n20130rv.s04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20130/S3

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-130/S-003

JAN 14 1998

Parke-Davis Pharmaceutical Research
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Attention: Mary E. Taylor
Worldwide Regulatory Affairs

Dear Ms. Taylor:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Estrostep (norethidrone acetate and ethinyl estradiol tablets, USP)

NDA Number: 20-130

Supplement Number: S-003

Date of Supplement: December 23, 1997

Date of Receipt: December 29, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 27, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-130/S-003
HFD-580/Div. Files
HFD-580/CSO/

SUPPLEMENT ACKNOWLEDGEMENT

Pharmaceutical Research
2800 Plymouth Road Phone: (313) 996-7000
Ann Arbor, MI
48105

PARKE-DAVIS

ORIGINAL

December 23, 1997

NDA 20-130
Ref. No. 38
Estrostep® (norethindrone acetate and ethinyl estradiol tablets, USP)

NDA NO. 20-130 REF. NO. 003
NDA SUPPL FOR SLR

Re: Phase IV Commitment Labeling Supplement

I have a Desk copy under review
3/18/98

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Document Control Room 12B45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A. ☐ MEMO

CSO INITIALS 2/12/99 DATE

Dear Dr. Rarick:

Reference is made to our New Drug Application (NDA 20-130) for Estrostep-21 (norethindrone acetate and ethinyl estradiol) Tablets, and Estrostep-Fe (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate) tablets.

Reference is also made to the approval letter dated October 9, 1996 (Attachment A), requesting additional supplemental labeling revisions as a Phase IV commitment. In that letter, the Agency requested that we conduct a multiple dose biopharmaceutics study which was specified in our submission dated April 9, 1996.

Reference is also made to our submission dated November 7, 1996, which contained a multiple dose biopharmacetutics study entitled, "A Single- and Multiple-dose Pharmacokinetic Study of Estrostep 1/20, 1/30, and 1/35". The protocol was accepted by the Division on December 27, 1996.

This supplement provides for the following information to fulfill our first and second Phase IV commitments outlined in the Agency's approval letter dated October 9, 1996:

Item 1. To conduct a multiple dose biopharmaceutics study designed to address the deficiencies discussed with the Division of Biopharmaceutics. You also agreed to submit the protocol within 30 days after approval. The study should be completed within one-year following your receipt of the Agency's comments on the protocol. The study should use the marketed tablets and should incorporate dosing regimens of the product consistent with its labeling.

Item 2. To update the ***CLINICAL PHARMACOLOGY*** *section of the labeling using data from the above study bioavailability and pharmacokinetics values and other relevant information (metabolism and excretion) upon completion of the above study.*

(Note: As a result of our proposed changes to the Clinical Pharmacology section of the labeling, changes to the PRECAUTIONS-DRUG INTERACTIONS subsection, DOSAGE AND ADMINISTRATION section and also the DETAILED PATIENT PACKAGE INSERT have been made.)

The following information has been included in this supplemental application for your review:

- Annotated Labeling, Volume 1
- Running Text Version of the Proposed Labeling Revisions, Volume 1
- References to Support Proposed Labeling, Volume 1-5

The references included in this supplemental application are publications, approved package inserts, and issued research reports. The dates of when the research reports were submitted to the Agency for review are included in the annotated labeling under the Rationale/Source column.

As requested by Ms. Christina Kish on November 6, 1997, electronic copy in WordPerfect Version 5.2 of the proposed package insert is attached (Attachment B). The revisions submitted in this pending supplement are included in this version.

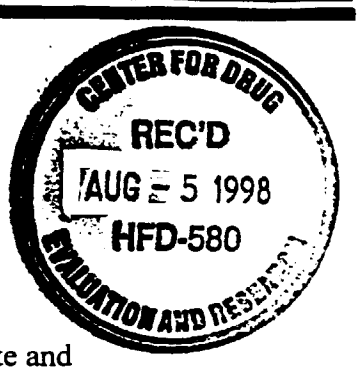
Also, as requested by the Agency's letter dated December 27, 1996, an electronic copy of the final study report in Microsoft Word 95, and ASCII files for the raw data for RR 744-00376 is also attached (Attachment B). The diskettes have been scanned for all known computer viruses using MacAfee V 3.03 for NT software.

Pharmaceutical Research
2800 Plymouth Road Phone (734) 622-7000
Ann Arbor MI
48105

PARKE-DAVIS

ORIGINAL

NDA SUPP AMEND
SLK-003
FB



August 4, 1998

NDA 20-130
Ref. No. 40
Estrostep® (norethindrone acetate and ethinyl estradiol, USP) Tablets

Re: Response to Information Request
Regarding S-003

Review completed on 10/2/98.
VRJ 11/17/98

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

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

Dear Dr. Rarick:

Reference is made to our approved New Drug Application (NDA 20-130) for Estrostep® (norethindrone acetate and ethinyl estradiol, USP) Tablets for oral contraception. Reference is also made to Supplement S-003 submitted December 23, 1997, and the telephone conversation between Christina Kish of your office and Robin Pitts of Parke-Davis on July 28, 1998.

We included in the supplement a research report describing the effect of food on the bioavailability of norethindrone acetate and ethinyl estradiol tablets. The study described in the research report used the proposed market image 1-mg norethindrone acetate and 10µg ethinyl estradiol FemHRT tablets (lot CX-0700695). Clinical studies with FemHRT tablets are conducted under IND Estrostep and FemHRT tablets are norethindrone acetate and ethinyl estradiol tablets, USP and meet the USP monograph requirements for assay, and dissolution. Since the formulation and dissolution profile of Estrostep are similar to those of FemHRT (see below), we believe that the results obtained with FemHRT tablets also apply to Estrostep tablets.

The formulations of Estrostep and FemHRT are similar. The FemHRT tablets used in the study were manufactured with a 5% ethinyl estradiol (EE) overage. The current approved Estrostep formulation has no EE overage. The formulations for both Estrostep and FemHRT used in this study are included in Attachment 1.

There are manufacturing process differences between FemHRT and Estrostep. The solids processor, The order of excipient addition and the drying processes are different. The manufacturing process for Estrostep tablets, reproduced from the April 9, 1996 Amendment to the NDA, is provided in Attachment 2. The manufacturing process for FemHRT tablets is provided in Attachment 3.

Twelve unit dissolution profiles sampled at 15, 30, 45, and 75 minutes for representative batches of Estrostep tablets were provided in NDA submissions on March 26, 1997 and April 7, 1997. These are reproduced in Attachment 4. The first page of the Attachment has the average values for each time point for each lot. The individual tablet results for each lot are shown in the following pages. A twelve unit dissolution profile for FemHRT tablet lot CX-0700695 is provided in Attachment 5. Both products dissolve rapidly, with nearly complete dissolution in fifteen minutes. Results at thirty minutes and later are essentially the same. The dissolution apparatus and medium are the same for both tablets. The methods use different columns. Estrostep uses a This narrow bore column is necessary because the amount of EE in FemHRT tablets is much less than in Estrostep tablets.

If you have any questions or comments regarding this submission please contact me at 734/622-7399 or FAX 734/622-7890, or Dr. Sean Brennan at 734/622-7596.

Sincerely,

Leslie Bloom

Leslie Bloom, Ph.D.
Director
Worldwide Regulatory Affairs

LB\ll\rm
t:\nda\20-130\080498-40

Attachments

Desk Copy: Dr. V. Jarugula, HFD-850

Pharmaceutical Research
2800 Plymouth Road Phone: 734.622.7000
Ann Arbor MI
48105

PARKE-DAVIS

ORIGINAL

~~NEW CORRESP~~
SUPPL NEW CORRESP
5-003-NC

February 22, 1999

NDA 20-130/S-003
Ref. No. 44
Estrostep® (norethindrone acetate and ethinyl estradiol tablets, USP)

Re: Intent to Amend

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 23 1999
HFD-580

Dear Dr. Rarick:

Reference is made to our approved NDA 20-130 for Estrostep® (norethindrone acetate and ethinyl estradiol tablets, USP). Reference is also made to FDA approvable letter dated February 12, 1999 for the above referenced application. Pursuant to 21 CFR 314.110, please be advised that we intend to amend the application.

If you have any questions or require additional information, please do not hesitate to contact me at 734/622-1537 or via FAX at 734/622-3283.

Sincerely,

Cheryl Beal Anderson, PharmD.
Manager
Worldwide Regulatory Affairs

CBA\dp
02-22-1999\RN-044\20-130\CI-0376\Letter

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS 2/26/99 DATE

Noted 2/25/99