CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-276

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-276	**Submission Dates:**
Brand Name:	Estrostep®	Supplemental NDA: 06/30/00 Amendments 02/22/01, 04/06/01
Generic Name:	Norethindrone acetate (NA) and Ethinyl Estradiol (EE)	**E-mail Communications** 01/30/01 and 03/21/01
Dosage Form:	Tablets	
Strength:	1mg/20mcg, 1mg/30mcg, 1mg/35 mcg	
Applicant:	Parke-Davis Pharmaceutical Research Ann Arbor, MI	
Priority Classification:	6S	
OCPB Division:	DPEIII	
Reviewer:	Abimbola Adebowale Ph.D. Elena Mishina Ph.D.	
Team Leader:	Dennis Bashaw Pharm.D.	

TABLE OF CONTENTS

RECOMMENDATIONS AND COMMENTS

Based on the exploratory data analysis submitted by the applicant the plasma concentrations of ethinyl estradiol and norethindrone after clinical use of Estrostep® tablets in patients with moderate acne vulgaris were found to be comparable between adults (≥ 18 years old) and adolescents (<18 years old) who have achieved menarche. The evaluation of the effect of age on the pharmacokinetic parameters of ethinyl estradiol and norethindrone was not conclusive due to discrepancies in the approaches used for the NONMEM analysis. The implication of this is that the labeling changes proposed by the applicant can only include the results of the plasma concentrations and not the pharmacokinetic parameters.

However, in this NDA the dosing regimen and target population (i.e., females who have achieved menarche) has not changed for the acne indication and, there was no outstanding clinical pharmacology and biopharmaceutics issues from approved NDA 21-130. Based on the aforementioned and the plasma concentration data the applicant has met the requirements outlined in 21CFR 320, and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. Also please convey the comments on page 18 for future applications.

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

I. Background and Introduction

Estrostep® consists of the active ingredients ethinyl estradiol (EE) and norethindrone acetate (NA). Estrostep ® tablets are currently approved (NDA 20-130, 10/09/96) and marketed for use as a graduated-estrogen-dose oral contraceptive. This supplemental NDA under review is a request by the applicant for approval of a new indication of use for the approved and marketed Estrostep® tablets for treatment of moderate acne vulgaris in females between 14 and 49 years of age, who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.

Oral contraceptive pills (OCPs) are believed to reduce androgen mediated sebum production involved in the development of acne. The proposed mechanisms is the suppression of gonadotrophin secretion, thereby decreasing ovarian androgen secretion and also probably increase the concentration of sex hormone binding globulin (SHBG), reducing the amount of free androgen available.

II. Overview of the NDA

In this application the applicant did not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages or dosing regimen for approved Estrostep® tablets. In section 6 of this NDA the applicant has cross-referenced approved NDA 20-130 for the human pharmacokinetics and biopharmaceutics data that was characterized in women. However, the target populations for Estrostep® in the treatment of acne include adolescents and women. In light of this the applicant included a population pharmacokinetic report (RR-REG 764-03375) to characterize the effect of age (adolescents vs. adult women) based on sparse sampling from a subset of patients in the clinical trial (protocol 376-403) in this submission. The applicant also included efficacy and safety data from 2 randomized, double-blind, placebo-controlled trials in the treatment of adolescent girls and women with moderate acne vulgaris (protocol 376-403 and 376-404) in support of the indication of Estrostep ® in the treatment of moderate acne vulgaris.

III. Pharmacodynamics

Following multiple dosing of Estrostep® tablets to patients with moderate acne vulgaris spanning the ages of 14-48 (N =57) an increase ~ 2-fold in sex hormone binding globulin (SHBG) serum concentrations from baseline was obtained in Study 376-403. The data submitted suggests that the increase in SHBG serum concentrations from baseline was numerically higher in the healthy volunteers (~3-fold) than the patients (~2-fold) after 4 and 6 cycles respectively. However, when the variability associated with the SHBG serum concentrations is considered the difference is minimal.

IV. Pharmacokinetics

The plasma concentration-time profiles observed in healthy volunteers following administration of Estrostep® containing 35 mcg of EE superimposed on the sparse data from patients suggests that, the plasma concentrations are consistent between healthy volunteers and patients with moderate acne vulgaris. The information submitted also demonstrated that the plasma concentrations of EE and norethindrone (N) in adults (≥ 18 years old) and adolescents (< 18 years old) were comparable, indicating that age does not influence the plasma concentrations

of EE and N following clinical use of Estrostep® tablets for acne. The total number of plasma concentrations for EE and N outside the 90% CI of the adult plasma concentrations were less than 20% indicating that the number of extreme values was minimal.

The estimation of the parameters for the targeted patient population in the population pharmacokinetics analysis submitted by the applicant was found not to be conclusive by the pharmacometrics reviewer (Dr. E. Mishina) due to discrepancies in the approaches used for the NONMEM analysis. Therefore, an evaluation of the effect of age on the pharmacokinetic parameters of EE and N by comparing the pharmacokinetic parameters in adolescents (< 18 years old) and adults (≥ 18 years old) could not be made with the data submitted.

However, a preliminary review of the frequency of all adverse events between adolescents and adult women with acne vulgaris suggested that there were no apparent differences. The applicant reported that in Estrostep®-treated subjects (N = 297), 54% of those <18 years old and 61% of those ≥ 18 years old experienced an adverse event. These results suggested that any age related differences in the pharmacokinetics of EE and N were not reflected in the frequency of adverse events.

V. Analytical Methods

The analytical methods used for the determination of EE and N in plasma were acceptable.

APPEARS THIS WAY
ON ORIGINAL

QUESTION BASED REVIEW

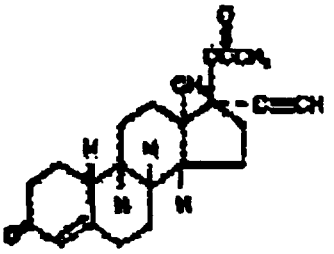
I. Introduction and Background

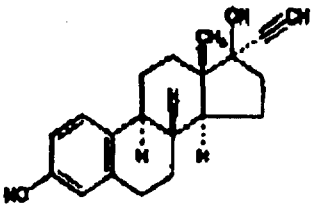
What are the physicochemical, formulation and pharmacological characteristics of the drug/drug products?

Since the applicant stated that this supplemental NDA does not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages or dosing regimen for Estrostep®, this information was cross referenced to approved NDA 20-130. A brief summary of the same information is provided below:

Physiochemical properties of the drug substances(s):

Estrostep® consists of the active ingredients ethinyl estradiol (EE) and norethindrone acetate (NA). The physiochemical properties of (NA) and (EE) are as follows:





Drug Name	Norethindrone Acetate	Ethinyl Estradiol
Chemical Name	17-hydroxy-19-nor-17α-pregn-4-en-20yn-3-one acetate	19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
Molecular formula	$C_{22}H_{28}O_3$	$C_{20}H_{24}O_2$
Molecular weight	340.47	296.41
Solubility	Practically insoluble in water. Soluble in organic solvents	Practically insoluble in water. Soluble in organic solvents

Formulation:

The applicant states that Estrostep ® tablets consists of three different types of tablets as follows containing 1 mg of norethindrone acetate (NA) and a graduated dose sequence of ethinylestradiol (EE) with the quantitative composition reproduced in the table below:

	1/20 Tablets	1/30 Tablets	1/35 Tablets
Ingredients	**Amount per Tablet (mg)**		
Norethindrone Acetate, USP	1.00	1.00	1.00
Ethinyl Estradiol, USP			
[redacted] Lactose [redacted]			
Starch, [redacted]			
Microcrystalline Cellulose, NF			
Calcium Stearate, NF			
[redacted]			
Total	70.00	70.00	70.00

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

The graduated sequence of EE consists of 5 white triangular shaped tablets containing 20 mcg of EE, 7 white square shaped tablets containing 30 mcg of EE, 9 white round shaped tablets containing 35 mcg of ethinyl estradiol. In addition the Estrostep ®Fe tablets also contains 7 brown tablets consisting of ferrous fumarate.

Proposed Mechanism of Action:

Oral contraceptive pills (OCPs) are believed to reduce androgen mediated sebum production involved in the development of acne by 2 mechanisms. They suppress gonadotrophin secretion, decreasing ovarian androgen secretion and they increase the concentration of sex hormone binding globulin (SHBG), reducing the amount of free androgen available. The applicant stated that recent data have indicated that Estrostep® increases SHBG 2- to 3-fold and lowers free testosterone 47% to 64%, indicating minimal androgenic activity.

Proposed Therapeutic Indication:

Estrostep® tablets are intended for treatment of moderate acne vulgaris in females between 14 and 49 years of age, who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.

Proposed Dosage and Administration:

For Estrostep ® one tablet daily for 21 days and then 7 days off (i.e. no tablets) with the graduated sequence of ethinylestradiol (EE) over a 21-day period of (20mcg x 5days, 30 mcg x 7 days, and 35 mcg x 9 days). For Estrostep ® Fe tablets one white tablet daily for 21 days and then 1 brown tablet daily for 7 days.

II. Overview of the Studies included in the NDA

The original NDA 20-130 for Estrostep® was approved on October 9, 1996, for oral contraception with a Phase IV commitment to do a multiple dose pharmacokinetic study, revise the labeling and, provide dissolution profiles using the USP dissolution method for 3 production lots of each strength (1/20, 1/30 and 1/35). The sponsor fulfilled their Phase IV commitments for the multiple dose study and the label revision (reviewed by Dr. V. Jargula 10/2/98 and 3/10/99) and the provision of dissolution profiles (reviewed by Dr. A. Dorantes dated 07/1/97). There are currently no outstanding Phase IV commitments from the office of clinical pharmacology and biopharmaceutics for NDA 20-130 (confirmed with Dr. A Parekh on 08/02/00).

In the FDA minutes from the Pre-NDA meeting held on January 6,2000, although there was no biopharmaceutics FDA participant physically present, under the subheading "Bioharmaceutics" it was stated that "Biopharmaceutics reported that there are no outstanding issues at this time". This was based on the fact that no relevant biopharmaceutic issues unique to the acne indication was expected since the applicant stated that this NDA does not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages or dosing regimen for Estrostep®. However, in this NDA the sponsor is proposing to include additional labeling with regards to pharmacokinetics of the components of Estrostep in adolescents.

In section 6 of this NDA the applicant has referred to approved NDA 20-130 for the human pharmacokinetic data. and biopharmaceutics data that was characterized in women. However, the target populations for Estrostep® in the treatment of acne include adolescents and

women. In light of this the applicant included a population pharmacokinetic report (RR-REG 764-03375) to characterize the effect of age (adolescents vs. adult women) based on sparse sampling from a subset of patients in the clinical trial (protocol 376-403) in this submission. The applicant also included efficacy and safety data from 2 randomized, double-blind, placebo-controlled trials in the treatment of adolescent girls and women with moderate acne vulgaris (protocol 376-403 and 376-404) in support of the indication of Estrostep ® in the treatment of moderate acne vulgaris.

III. Summary of the pharmacokinetics of Estrostep® from approved NDA 20-130

Absorption: In published literature it was reported that norethindrone acetate (NA) and ethinyl estradiol (EE) are rapidly absorbed, with maximum plasma concentrations of norethindrone (N) and ethinyl estradiol occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol. NA appears to be completely and rapidly deacetylated to N after oral administration, because the disposition of NA is indistinguishable from that of orally administered N.

Following the multiple dose administration (Study 376-397, N = 17 healthy women) the mean steady-state plasma concentrations of norethindrone (N) for the 1/20, 1/30, and 1/35 tablet strengths increased as ethinyl estradiol (EE) dose increased over the 21-day dose regimen. Mean (SD) steady-state pharmacokinetic parameters following chronic administration of Estrostep® are shown in the table inserted below:

Norethindrone Acetate/Ethinyl Estradiol Dose	Cycle Day	Cmax	AUC	CL/F	SHBG[b]
Norethindrone (N)					
mg/μg		ng/mL	ng·hr/mL	mL/min	nmol/L
1/20	5	10.8	81.1	220	120
		(3.9)	(28.5)	(137)	(33)
1/30	12	12.7	102	166	139
		(4.1)	(32)	(85)	(42)
1/35	21	12.7	109	152	163
		(4.1)	(32)	(73)	(40)
Ethinyl Estradiol (EE)					
mg/μg		pg/mL	pg·hr/mL	mL/min	nmol/L
1/20	5	61.0	661	549	
		(16.8)	(190)	(171)	
1/30	12	92.4	973	546	
		(26.9)	(293)	(199)	
1/35	21	113	1149	568	
		(44)	(372)	(219)	

[a] Cmax=Maximum plasma concentration; AUC(0-24) Area under the plasma concentration-time curve over the dosing interval; CL/F=Apparent oral clearance

[b] Mean (SD) baseline value=55 (29) nmol/L

The increase in N concentrations was due to dose-dependent increases in serum sex hormone binding globulin (SHBG) concentrations. Mean steady-state plasma concentrations of ethinyl estradiol were dose proportional in the range of doses administered (20, 30, and 35). The mean plasma free testosterone concentrations 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.

In a food effect and relative bioavailability study administration of two 1/10 strength, NA/EE with a high fat meal decreased rate, but not extent, of EE absorption. The Cmax of EE was decreased by 29%. The rate of absorption of N was slightly decreased but the extent of absorption was increased by 27% following administration with food.

Distribution Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism: Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine.

Excretion: Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of Estrostep® are approximately 13 hours and 19 hours, respectively.

IV. Clinical Pharmacology:

Safety and Efficacy:

Q. What are the clinical endpoints, surrogate endpoints or biomarkers (PD) used to assess efficacy and safety?

Efficacy: Estrostep was evaluated in 298 healthy subjects age 14-49, ≥ I year post menarche with moderate facial acne with 20 to 100 comedones and 20 to 65 inflammatory lesions with no more than 5 nodules, in 2, nearly identical clinical trials (376-403 and 376-404). To demonstrate efficacy, Estrostep-treated subjects must have shown significant improvement in 2 of 3 lesion counts (total number of acne lesions, inflammatory lesions, and comedones from baseline to study exit) relative to placebo and these results must be supported by the Facial Acne Global Assessment Score (An investigator 7-point assessment with the following categories: absent, minimal, mild, mild to moderate, moderate, marked and severe). The secondary endpoints included total and free testosterone, SHBG, and DHEA-S level changes from baseline to exit at selected sites only.

Safety: Adverse events (e.g. metrorrhagia, headache, nausea), pregnancy tests, changes in clinical laboratory parameters (e.g., total bilirubin, glucose levels,) systolic and diastolic blood pressure, weight, plasma concentrations of EE and N.

Analytical Methods:

Q. Were the analytical methods used to determine plasma concentrations of ethinyl estradiol (EE) and norethindrone (N) acceptable?

Yes, the analytical methods were acceptable.

Exposure-Response:

Efficacy:

Q. What are the exposure response relationships for efficacy and safety in patients with acne vulgaris?

An evaluation of the primary efficacy parameter (i.e. change in lesion counts) is currently under review by the medical reviewer. The data for one of the secondary efficacy parameters, sex hormone binding globulin (SHBG) serum concentration was however, included in the human pharmacokinetics and biopharmaceutics section of the NDA. These data showed that following multiple dosing of Estrostep® tablets to patients with moderate acne vulgaris spanning the ages of 14-48 (N =57) an increase ~ 2-fold from baseline was obtained in Study 376-403. The increase in SHBG serum concentrations from baseline was numerically higher in the healthy volunteers (~3-fold) than the patients (~2-fold) after 4 and 6 cycles respectively. However, when the variability associated with the SHBG serum concentrations is considered the difference is minimal.

Safety:

Q. Was there a difference in the frequency of all adverse events (AE's) between women and adolescent patients with acne vulgaris?

A preliminary review of the frequency of all adverse events between adolescents and adult women with acne vulgaris suggested that there were no apparent differences. The applicant reported that in Estrostep®-treated subjects (N = 297), 54% of those <18 years old and 61% of those ≥ 18 years old experienced an adverse event. In the <18 year age group, infection (17%); metrorrhagia (16%); abdominal pain (7%), headache (6%); and pharyngitis (6%) nausea (1%); flu syndrome (4%) and accidental injury (4%), were the most frequently reported AEs. In the ≥18 years old age group, metrorrhagia (18%); infection (14%); nausea (8%); flu syndrome (7%); headache (7%); and accidental injury (5%), abdominal pain (3%) and pharyngitis (3%)

were the most frequently reported AEs. These results therefore suggest that the frequency of adverse events between adolescents and adult women with acne vulgaris were similar.

Pharmacokinetics:

Q. Are the PK characteristics of the Estropstep in healthy volunteers and patients with the target indication comparable?

The plasma concentration-time profiles observed in healthy volunteers following administration of Estrostep® (containing 35 mcg of EE) superimposed on the sparse data from patients with acne vulgaris (shown in the graphs inserted below Figures 2 and 11)

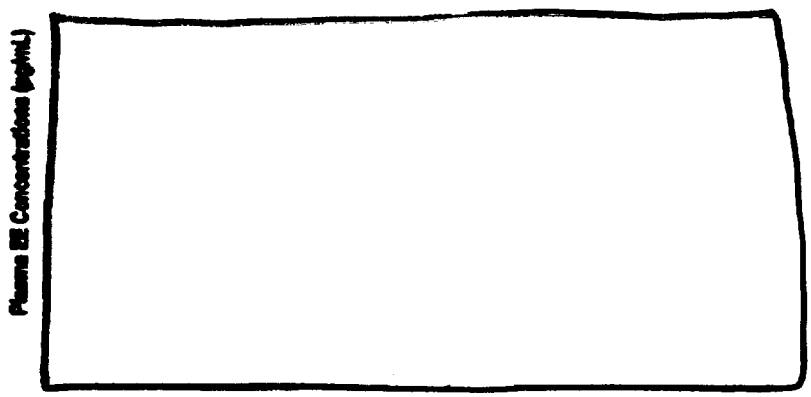


Figure 2. **Log Plasma Ethinyl Estradiol (EE) Concentration Versus Time Profile in Healthy Women in Study 376-397 (Lines) and in Study 376-403 in Adults (≥18 Years of Age) (Open Circles) and Adolescents (<18 Years) (Black Circles)**

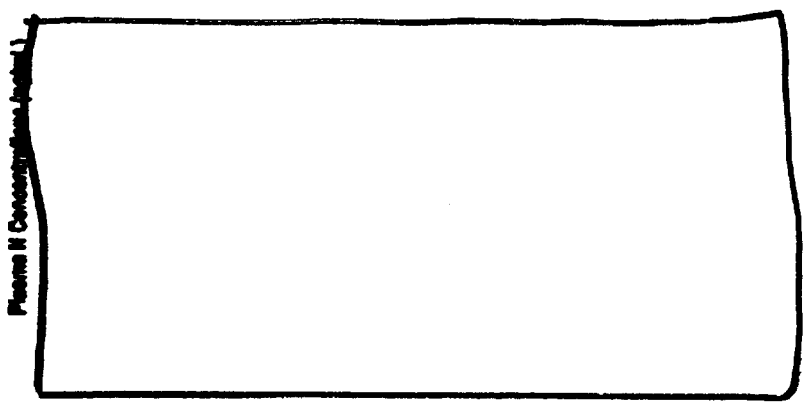
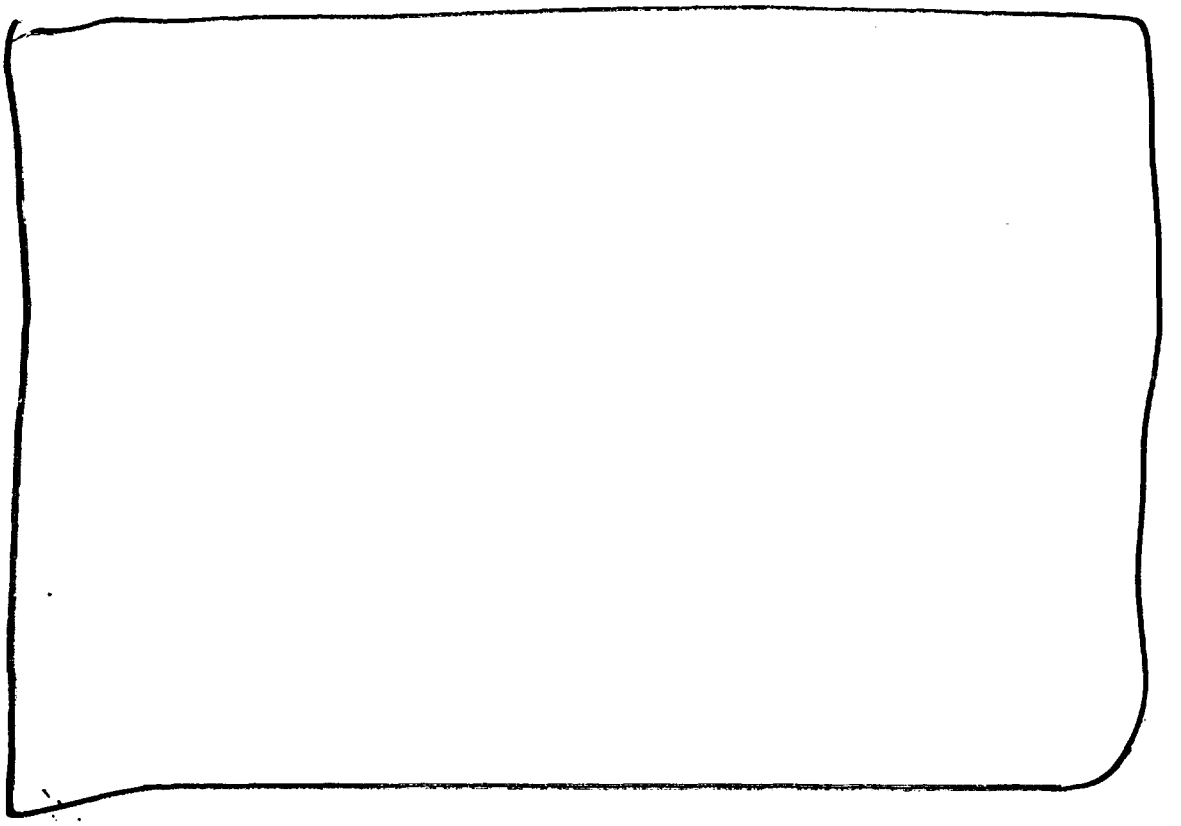


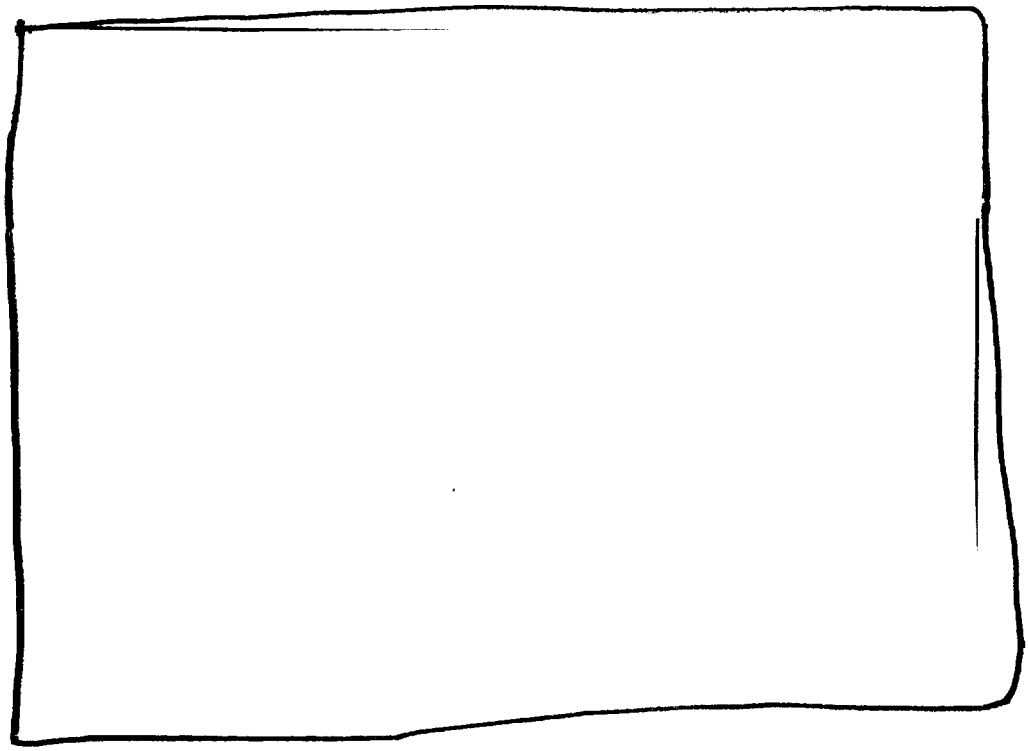
Figure 11. **Log Plasma Norethindrone (N) Concentration Versus Time Profile in Healthy Women in Study 376-397 (Lines) and in Study 376-403 in Adults (≥18 Years of Age) (Open Circles) and Adolescents (<18 Years) (Black Circles)**

Although the graphs above show that there were some observed concentrations in the patient population that were above and below the profiles in healthy volunteers, these did not appear to show any particular trend that would suggest differences in the plasma concentrations between the two populations.

Q. Does the intrinsic factor age influence the PK of the Estrostep® and what is the impact on exposure and is there a need to adjust dose/ dosage regimens?

The plasma concentrations obtained in the adolescent patient population were comparable to that obtained in the adult patient population as shown in the plasma concentration time profiles below suggesting that age does not influence the plasma concentrations of EE and N following clinical use of Estrostep® tablets for acne. Reproduced below are the graphical representation of plasma concentrations of EE and N obtained from the raw data in patients with acne vulgaris which are exactly the same as the patient log plasma concentration vs. time profiles in Figures 2 and 11 above without the plasma concentration time profiles from healthy volunteers superimposed on the sparse data. (Details of the Internal Meetings, Resolutions and Communications with the sponsor with regards to the additional analysis of the plasma data in the target population using exploratory analysis due to flaws in the NONMEM analysis in RR-REG 764-03375 are included in the Appendix pages 26-32).





The graphs above show that the plasma concentrations obtained in the adolescent patient population were interspersed amongst the plasma concentrations obtained in the adult population with no apparent trend or differences suggested. Reproduced in the table below are the summary of EE and N concentration data in adult and adolescents using the specific time intervals.

Ethinyl Estradiol Plasma Concentrations in Adults and Adolescents

	Adult ≥ 18 years old				Adolescent , 18 years old		
Time Interval (hr)	**N**	**Mean (SD) (pg/mL)**	**Median (pg/mL)**	**90% CI**	**N**	**Mean (SD) (pg/mL)**	**Median (pg/mL)**
0-1	11	58.3 (70.0)	29.7	0-178	4	71.55 (15.4)	65.1
1-3	31	75.6 (50.5)	72.4	0-158.5	7	41.93 (14.71)	54
3-6	16	91.3 (45.8)	92.9	27.9-162.3	6	78.44 (22.26)	103
6-12	31	47.8 (16.9)	46.8	26.3-80.5	17	53.88 (9.5)	51.1
12-18	33	46.2 (42.2)	38.1	0-137	9	46.21 (12.17)	38.2
18-24	37	32.3 (18.5)	31.0	3.9-66.7	14	31.53 (17.06)	10.75

Norethindrone Plasma Concentrations in Adults and Adolescents

	Adult ≥ 18 years old				Adolescent , 18 years old		
Time Interval (hr)	**N**	**Mean (SD) (ng/mL)**	**Median (ng/mL)**	**90% CI**	**N**	**Mean (SD) (ng/mL)**	**Median (ng/mL)**
0-1	11	4.73 (5.52)	3.22	0-14.55	4	9.15 (2.95)	8.20
1-3	31	8.14 (5.99)	8.83	0-17.85	7	5.70 (2.38)	4.48
3-6	16	8.53 (5.17)	7.66	2.3-17.88	6	6.97 (1.95)	8.99
6-12	31	5.04 (2.86)	4.95	1.35-10.46	17	5.14 (1.08)	4.46
12-18	33	4.24 (4.33)	3.11	0-12.15	9	3.68 (0.54)	3.72
18-24	37	3.60 (2.88)	2.68	0.06-8.28	14	1.76 (0.61)	0.995

The data in the table above show that for the time intervals within the dosing interval (0-24 hours) the mean plasma concentrations for EE and N in the adolescent patient population were comparable to that obtained in the adult population when the variabilities associated with the mean were considered. Numerically, the total number of EE 8/61 (13.1%) concentrations and N 4/61 (8.2 %) concentrations outside the 90% confidence intervals were less than 20% indicating that the number of extreme values was minimal.

Inserted below (on page 17) is the graphical representation of the Median and 5^{th}-95^{th} percentiles (90% CI) of EE and N concentrations over specific time intervals with observed individual concentrations of adolescent patients overlaid on the plots.

Pharmacokinetic Parameters:

Since the estimation of CL/F (oral clearance) and V_c/F (central volume of distribution) for the targeted patient's population (sparse data) was not conclusive according to the pharmacometrics reviewer (Dr. E. Mishina) due to flaws in the approaches used for the NONMEM analysis, the population pharmacokinetics of EE and N in women with moderate acne vulgaris was not assessed. Therefore the primary objective of the study to an evaluate the effect of age on the pharmacokinetic parameters on EE and N in women with moderate acne vulgaris who had achieved menarche could not be made (Please see pharmacometrics review in Appendix pages 33-38 for details).

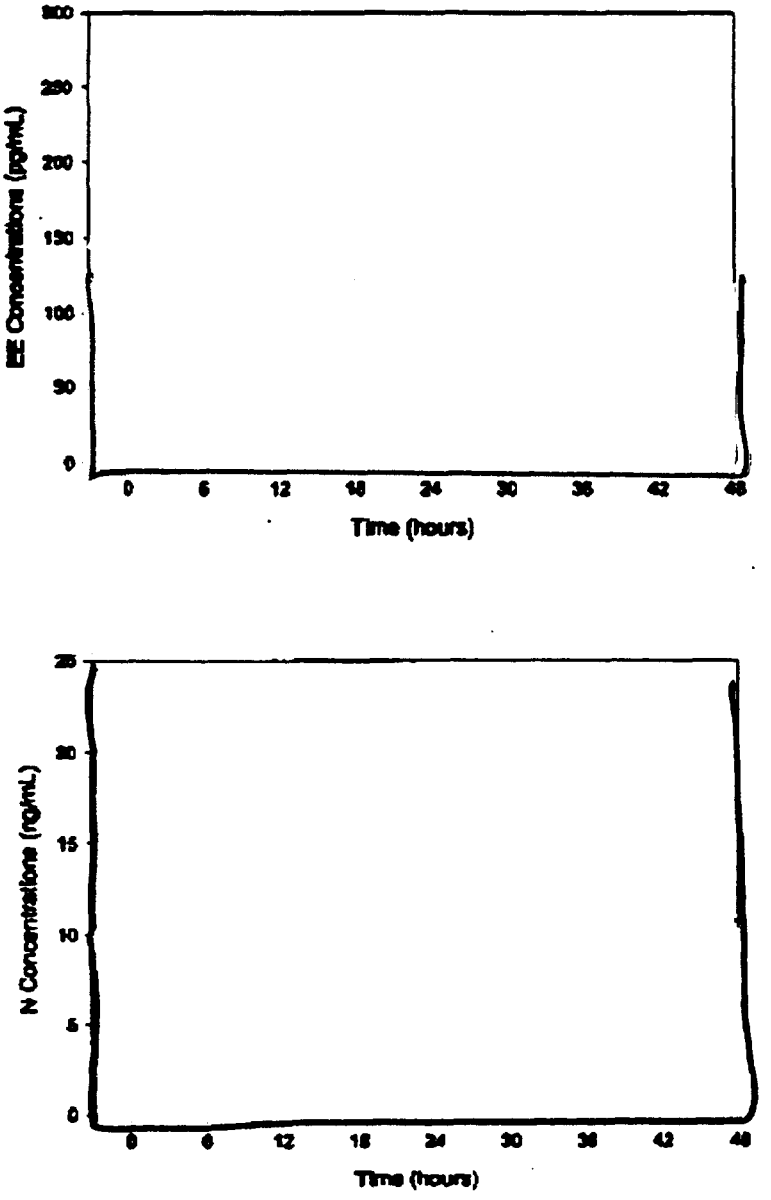


Figure: Median (dashed Line) and 5th-95th Percentiles (Solid Lines) of Ethinyl Estradiol (EE: Upper Panel) and Norethindrone (N; Lower Panel) Concentrations over 6 Time Intervals from Adult Patient Data (≥ 18 years old) with Individual Concentrations (Solid Circles) in Adolescents (< 18 years old)

LABELING RECOMMENDATIONS

The proposed label included in the proposed package insert under the subheading "Special Populations" is reproduced below:

COMMENTS FOR APPLICATION TO FUTURE SUBMISSIONS

The following comments were summarized from the pharmacometrics review by Dr. E Mishina (A copy is attached in the Appendix on Pages 33-38)

1. The estimation of the pharmacokinetic parameters (clearance and volume of distribution) for the targeted patient population was not conclusive. The applicant did not include full documentation of the variabilities associated with them and the goodness of fit of the targeted patient's population data to the model used to describe the pharmacokinetics of EE and N in healthy volunteers. In future submissions the applicant should report the output results for the patients' data and particularly the variabilities for the estimated pharmacokinetic parameters.
2. Since the sparse data file for the patient's population was not sufficient to perform a successful run for either EE or N, the approach of analyzing the rich data for the healthy volunteers and sparse data for patients may lead to erroneous estimates, especially if the sparse data is lacking in information. The residual error structure could be different between these two populations. These possible differences in the residual error structure can be evaluated by combining both data sets, including STUDY as a covariate and, coding the different residual error models for these data sets.
3. Although the applicant evaluated the influence of age by plotting the pharmacokinetic parameters vs. age, this did not allow for a statistically valid assessment. In future submissions, the applicant should also apply a covariate analysis by incorporating age as a covariate into the population model for a statistically valid assessment of the effect of age.

Abimbola O. Adebowale Ph.D.
Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D. _____

APPENDIX

APPENDIX I: REVIEW OF INDIVIDUAL STUDIES

STUDY ABSTRACT FORM Protocol No. 376-403

TITLE: Efficacy and Safety of Estrostep® (CI-376) in the treatment of Moderate Acne Vulgaris: A 6-month Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study
SPONSOR: Parke-Davis Pharmaceutical Research
Study Type: Efficacy and Safety with Sparse PK sampling **Protocol Number**: 376-403 **Investigators:** 22 Active Investigators **Site** 17 active study centers in the USA **Study Period:** September 11, 1998 to February 1, 2000 (6 months)
€ Single Dose [X] Multiple Dose
OBJECTIVE: To assess the efficacy and safety of Estrostep compared with placebo in the treatment of moderate acne vulgaris.
SUBJECTS: € Normal [X] Patients € Young € Elderly,. All had moderate acne vulgaris for a mean duration of 120 months IMPAIRED: € Renal € Hepatic
DESIGN: € Crossover [X] Parallel [X] Randomized [X] Placebo-controlled [X] Double-Blind WASHOUT:NA
DEMOGRAPHICS (entered/completed): Total N = # Males = 0 # Females = 298 (Estrostep 150, Placebo 148)
Mean (Range) Age (years) 24.48 (range 13 – 48) 22% < 18 years old and 66% were Caucasians, 14% were black, 12% were Hispanic, 3% were Asian and 3% were other. Body Mass Index (BMI): 25.01
TREATMENT: Once a day oral QD for 6 months, 28-day cycles as follows • 1 mg NA/20 mcg EE [lot # CJ0190298, CJ0630399, CJ1110898] for 5 days, • 1 mg NA/30 mcg EE [lot # CJ0200298, CJ0640399, CJ1120898] for 7 days, • 1 mg NA/35 mcg EE [lot # CJ0210298, CJ0650399, CJ1130898] for 9 days, and • 75 mg ferrous fumarate (lot # CJ0270398, CJ0660399) for 7 days. Placebo was administered the same way.
STUDY DESIGN Screening(Visit 1) Eligible Subjects Randomized to Treatment (6, 4-week cycles) Estrostep Cycle: 1 2 3 4 5 6 Placebo Visit: 2-3 4 5 6 7 8-10
€ Fasted 10 hours prior to dosing and 4 hours after dosing € Non-fasted € Food Study € High Fat Breakfast
EFFICACY: Primary Efficacy Parameter: Change in lesion counts (total, inflammatory and comedones), facial Acne Global Assessment Secondary Efficacy Parameters: Facial acne global assessment, subject's end of treatment self-assessment. Serum levels of total testosterone, free testosterone, sex hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEA-S) were determined at selected sites only. Acne Specific quality of life assessment, impact of acne on daily activities assessment SAFETY: Safety Parameters: Spontaneously reported adverse events, pregnancy tests, changes in clinical laboratory parameters, systolic and diastolic blood pressure, weight, Pharmacokinetic data by sparse sampling for plasma EE and N
SAMPLING: Plasma (10 mL) samples for determination of ethinyl estradiol and

norethindrone concentrations
SAMPLING TIMES: Visit 2 (pre-dose), and end of cycles 2 and 6 (visits 4 and 10) on days 18, 19, 10 and 21 during administration of the 1-mg NA/35 mcg EE dose of Estrostep®. Samples were also obtained on Visit 5, at early termination. Samples analyzed using population analysis methods. For SHBG, testosterone and DHEA-S samples were collected at Visit 2, 4 and 6 i.e. pre-dose, cycle 2 and 4

SUMMARY OF POP PK STUDY RESULTS: Plasma concentrations of EE and N were consistent across the age ranges evaluated.

Analytical Methods:

Population Pharmacokinetic Analysis Report RR-REG 764 03375

TITLE Population Pharmacokinetics of Estrostep® in Women With Moderate Acne Vulgaris (Protocol 376-403)

OBJECTIVE To characterize the population pharmacokinetics of ethinyl estradiol (EE) and norethindrone (N) following administration of Estrostep® in women with moderate acne vulgaris and characterize the effect of age on the pharmacokinetic parameters, particularly adolescent versus adult women

AUTHOR(S) D. Ouellet, E. A. Zegarac (Parke-Davis Pharmaceutical Research)

METHODS

Datasets: A dataset was created for the sparse sample data collected in study (376-403) which included the times of the last 3 doses prior to sample collection, the time of sample collection, plasma concentrations of EE and N, demographic and physiologic variables. A second dataset was created based on the steady-state data obtained previously in 17 healthy volunteers using extensive sampling (Study 376-397) and included similar variables as the patient dataset. For the covariate information, age, weight, height, baseline albumin, and baseline SHBG concentrations were recorded based on the value at the time of the first visit. SHBG was measured on Visits 4 and 10 in a subset of patients. These values were used to create a covariate for SHBG that changed with time.

Pharmacokinetic Analysis: Ethinyl estradiol and N pharmacokinetics in patients was characterized based on a population model developed in healthy volunteers (Study 376-397) using nonlinear mixed effects modeling (NONMEM). The population parameter estimates determined in healthy volunteers (mean and intersubject variability) were used as priors and bayesian estimates of oral clearance (CL/F) and central volume of distribution (Vc/F) were generated for each patient using the sparse data obtained in study 376-403.

Briefly for 376-397 the Phase IV multiple dose study, plasma samples for determination of EE and N concentrations were obtained using extensive sampling at steady state during a third cycle of Estrostep on Cycle Day 5 (1-mg NA/20-mcg EE dose), 12 (1-mg NA/30-mcgEE dose), and 21 (1-mg NA/35-mcg EE dose). Samples were obtained at timed intervals for 24 hours on Cycle Days 5 and 12 and for 48 hours on Cycle Day 21. Trough samples were obtained on Days 3, 4, 10, 11, 19, and 20. Data were also collected following a single dose but these data were not included in the analysis. SHBG was quantitated on Days 1, 5, 12, and 21. In creating the dataset, the SHBG value reported on these days was also carried over to previous days. For example, the value reported on Day 5 was also used on Days 3 and 4 when trough concentrations were measured since SHBG was not measured at each time point.

RESULTS AND DISCUSSION

Population Characteristics: A total of 130 patients enrolled in Study 376-403 were included in the NONMEM analysis. The characteristics of the healthy volunteer population used to build the model (376-397) and the patient population (376-403) are summarized in the table below:

Variable	Study 376-397 Healthy Volunteers (N = 17)	Study 376-403 Patients (N = 130)
Age (years)	31.4 ± 6.4 (20-39)	25.0 ± 8.2 (13-48)
Weight (kg)	80.5 ± 24.3 (52.6-141.2)	68.6 ± 16.7 (44.7-139.7)
Height (cm)	168 ± 7.3 (154-185)	165 ± 7.2 (130-180)
Baseline SHBG (nmol/L)	51.2 ± 22.3	78.3 ± 31.9
SHBG (nmol/L)	163 ± 39.8[b]	186 ± 69.4

Data expressed as mean ± SD (range).; [a]N = 61.; [b]SHBG reported on Cycle 4, Day 21 for Study 376-397. [c]SHBG reported on Visit 10 or termination visit for Study 376-403 (N = 57).

This shows that the age range of the patient population although higher at the upper range was also lower at the lower range going down to 13. The frequency distribution of the patients across ages demonstrated that thirty-one patients included in the data analysis were less than 18 years of age, representing 24% of the patient population.

The data submitted suggests that the increase in SHBG serum concentrations was more marked in the healthy volunteers (~3-fold) than the patients (~2-fold) after 4 and 6 cycles respectively. The mean change from baseline was 218.4% in healthy volunteers and137.5 %. The variability associated with the SHBG serum concentrations was about the same in the healthy volunteers and patients (44 and 41% respectively) at baseline. The variabilities were however higher in the patient population (37.3%) after a 6-cycles than the healthy volunteers (24%) after 4-cycles. The difference in time of sampling and the administrative structure in that the study in the healthy volunteers was at a single center, while that in the patients was at a multicenter could have added to the variabilitiy observed in patients. The clinical significance of this finding is unknown. The SHBG increase was consistent between adults and adolescents.

SHBG levels	Adolescents (13-17) (N = 13)	Adults (18-48) (N = 44)
Baseline SHBG (nmol/L)	79.69 ± 30.99	79.56±32.28
SHBG (nmol/L)	167.31 ± 97.62	188.60±59.28
Mean Change from Baseline	87.62 ± 100.06	109.05± 59.83
Mean % change	146.4 ± 199.80	169.7± 136.20

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46 page(s) of revised draft labeling has been redacted from this portion of the review.

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.