

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-870

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: 20-870

Compound: ALIATIS™ [estradiol/norethindrone acetate/day: 50µg /140µg (9 cm²) and 50µg/250µg (16 cm²)] Transdermal Systems

Sponsor: Rhone Poulenc Rorer Pharmaceuticals

Type of Submission: Original NDA and 4 Amendments

Date of Submission: August 7, 1997
June 13, 1998, Amendment BB
June 22, 1998, Amendment BB
June 23, 1998, Amendment BC
July 6, 1998, Amendment BB

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

I. Synopsis:

NDA 20-870 for Aliatis™ transdermal system [50 µg estradiol and 140 or 250 µg norethindrone acetate (NETA)/day] was submitted on August 7, 1997 by Rhone Poulenc Rorer Pharmaceuticals. The proposed therapeutic indications for this product are: treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The proposed therapeutic regimen is twice weekly (every 3.5 days) application of a single Aliatis™ transdermal system.

In support of NDA 20-870, the sponsor has submitted the following definitive pharmacokinetic and bioavailability studies:

1. RPR 106522D-104, evaluated the steady-state relative bioavailability of Aliatis Transdermal System (estradiol/norethindrone acetate/day) at three dose levels (50/140, 50/250, 50/400) and Menorest® 50.
2. RPR 106522D-122, evaluated the relative bioavailability of Aliatis patch (50/250) at two different body sites: abdomen vs. buttocks.
3. RPR 106522D-126, evaluated the relative bioavailability of RPR Estradiol/NETA patch at two dose levels (50/100 and 50/250) and Estragest®.

In addition to the above studies, the sponsor submitted four preliminary studies which were conducted to determine the final Aliatis formulation for clinical development. The formulation used in clinical testing is the same as the to-be-marketed formulation.

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-870, submitted on August 7, 1997 and its amendments, dated June 13, June 22, and June 23 1998. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments:

1. The proposed *in vitro* release specifications for estradiol and NETA are not acceptable, the recommended specifications are as follows:
2. Labeling should be modified as outlined in section IX, **Labeling-Comments**, page 16.
3. The proposed application sites of lower abdomen and buttocks are not bioequivalent. Additionally, the difference in bioavailability between the two sites was deemed clinically significant by the medical officer, Dr. Phil Price, of DRUDP (HFD-580). Therefore, the buttocks are not acceptable as an application site for Aliatis™ transdermal system.

Comments 1, 2 and 3 and recommendation should be communicated to the sponsor as appropriate.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 7/1/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 7/7/98

cc:

NDA 20-870
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-850 (L. Lesko)
HFD-340 (C.T. Viswanathan)
HFD-580 (J. Markow, P. Price)
CDR (Barbara Murphy For Drug)

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III. Background

Estradiol is the most active of the naturally occurring estrogens, which are formed by the ovarian follicles under the influence of the pituitary gland. Estrogens control the development and maintenance of the female sex organs, the secondary sex characteristics and the mammary glands. In women between the ages of 40 and 50, the ovarian function declines resulting in the cessation of menstruation (menopause). During the time leading to menopause, the decline in estrogen levels produce various symptoms in a large percentage of women. Those symptoms include hot flushes, inappropriate sweating, vaginal dryness, and atrophy of the breasts. Additionally, the long term deficiency in estrogen has been associated with osteoporosis.

Hormone replacement therapy (HRT) involves the administration of an estrogen (alone or in combination with a progestin) to ameliorate vasomotor and other symptoms associated with menopause, and the prevention of osteoporosis. Currently, HRT is administered mainly by the oral route or through the skin using transdermal delivery systems (TDS). Regardless of the route of administration, estradiol is cleared rapidly from the plasma. It has a terminal half-life of about 2 - 4 hours.

This NDA is for a combination transdermal patch which provides systemic estrogen replacement therapy by releasing 17β -estradiol (E2), and norethindrone acetate (NETA), a progestational hormone, through the skin.

IV. Formulation

ALIATIS™ is a solid matrix transdermal patch. Two sizes of patch are intended to be marketed; a 9 cm² size which delivers 50/140 µg/day E2/NETA and a 16 cm² size which delivers 50/250 µg/day E2/NETA. The patches are round and translucent, with a removable, pre-cut liner. Figure 1 illustrates ALIATIS™ patch and components. The compositions are listed in Table I.

Figure 1. Schematic representation of Aliatis patch and its components.

Table I. List of formulations used in the clinical and pharmacokinetic studies.

TARGET DELIVERY RATE		
Norethindrone acetate ($\mu\text{g}/\text{day}$)		
Estradiol ($\mu\text{g}/\text{day}$)		
INGREDIENT - mg/patch (%w/w)		
Norethindrone acetate, USP		
Estradiol, USP		
Povidone, USP		
Silicone Adhesive		
Acrylic Adhesive		
Dipropylene glycol		
Backing (mg/unit)		
Liner (mg/unit)		
TOTAL WEIGHT (mg/unit)		
PATCH SIZE (cm^2)	9	16

* Removed from the product during the drying process

Reviewer Comment

1. The clinically tested formulation and the "to be marketed" formulation are the same and they were manufactured at the same site.

V. In Vitro Drug Dissolution

The *in vitro* release methodology and the proposed specifications for ALIATIS™ are presented in Table II. Tables III and IV provide *in vitro* release data for the clinically tested batches.

Table II. Proposed Drug Release Method and Release Rate Specifications.

Apparatus Type		
Media		
Volume		
Speed		
Sampling Times		
Proposed Specifications*	Time Intervals (hours)	Specification (%)
		Estradiol NETA
Cumulative amount released per system over a time interval		

Table III. Dissolution profiles of clinically tested batches (Estradiol).

Lot Number	Patch	Batch Size (kg)	Percent label claim released [mean (\pm SD)]			
			Time (hours)	2	8	14
9411440	50/140			37.8 (0.19)	80.4 (0.73)	94.1 (0.79)
9411441	50/250			45.2 (0.50)	83.2 (0.79)	94.5 (1.11)
9503636	50/250			46.4 (0.73)	83.5 (1.17)	91.8 (1.16)

Table IV. Dissolution profiles of clinically tested batches (NETA).

Lot Number	Patch	Batch Size (kg)	Percent label claim released [mean (\pm SD)]			
			Time (hours)	2	8	14
9411440	50/140			83.5 (0.67)	102.9 (1.78)	103 (1.73)
9411441	50/250			86.1 (1.09)	99.4 (1.68)	100.7 (1.68)
9503636	50/250			79.9 (1.04)	94.1 (1.24)	94.5 (1.06)

Reviewer Comments

1. The proposed *in vitro* dissolution methods are acceptable.
2. The proposed *in vitro* release specifications for estradiol and NETA are not acceptable, the recommended specifications are as follows:

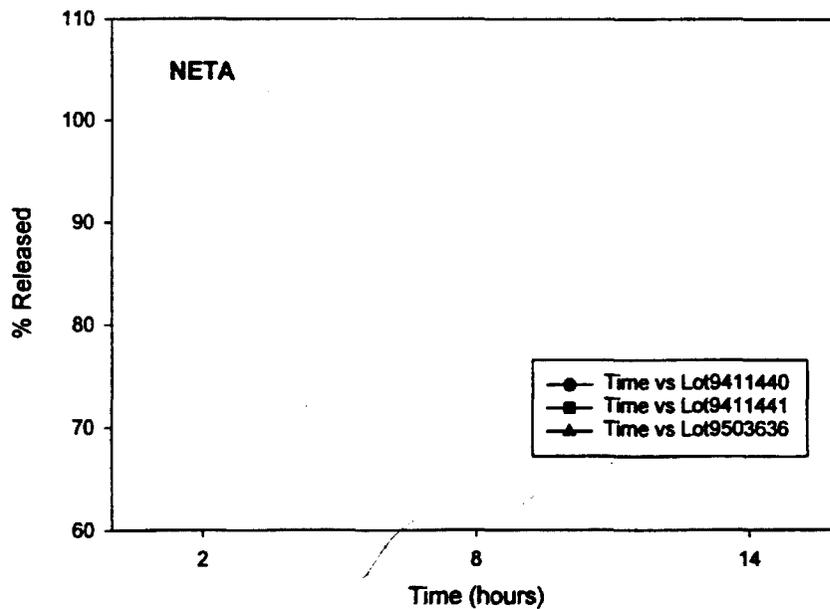
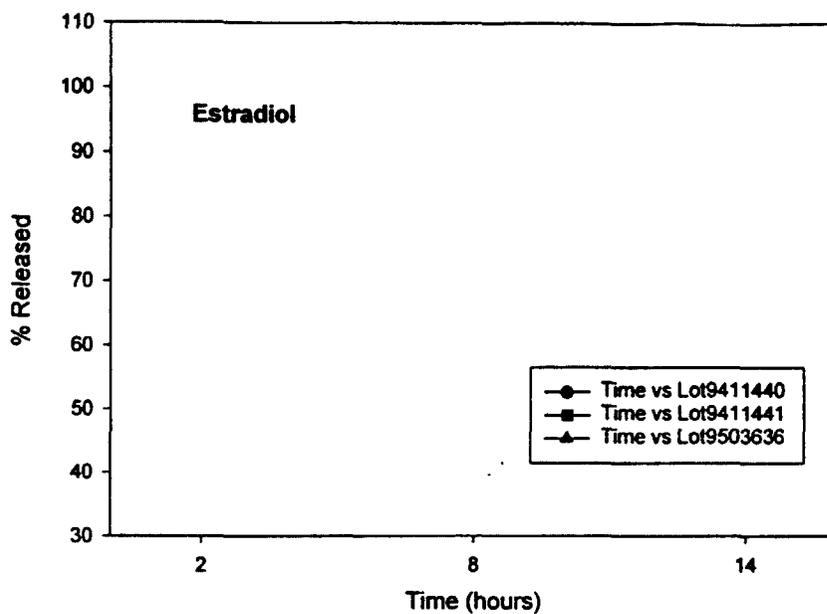


Figure 1. Dissolution profiles (estradiol and NETA) over time of clinically tested batches

VI. Analytical Methodology

Reviewer Comment

1. The analytical methods and validation for the estimation of estradiol and norethindrone concentrations in serum are acceptable.

VII. Clinical Pharmacology and Biopharmaceutics Studies

Table VII summarizes the clinical pharmacology and biopharmaceutic studies that were conducted to support the approval of ALIATIS.

Table VII. Summary of clinical studies.

Study No.	Study Design	Dosage Form	No. of Subjects
Pivotal Pharmacokinetic Studies			
RPR106522D-104	Open label, 4 way crossover, multi-dose, at three dose levels, and relative bioavailability comparison with Menorest® 50. Application site: abdomen	50/140, 50/250, 50/400, estradiol/ NETA transdermal system and Menorest® 50	40
RPR106522D-122	Open label, 2 way crossover, relative bioavailability, comparing application sites: abdomen vs. buttocks.	50/250 estradiol/ NETA transdermal system	18
RPR106522D-126	Open label, 3 way crossover, single application, relative bioavailability comparison with Estragest TTS. Application site: abdomen	50/140, 50/250, estradiol/NETA transdermal	18
Preliminary Studies			
RPR106522D-101	3 way crossover, pilot bioavailability study,	Patches under development (non-final formulation)	12
RPR106522D-102	3 way crossover, incomplete block design, bioavailability and linearity	Patches under development (non-final formulation)	24
RPR106522D-103	4 way crossover, incomplete block design, relative bioavailability	Patches under development and Menorest® 50	10
RPR106522D-105	3 way crossover, incomplete block design, pilot PK study	Patches under development	12

1. Protein Binding

No protein binding studies were done for this NDA; however, published literature indicates that estradiol is primarily bound to sex hormone binding globulin (SHBG), and to a lesser extent, to albumin; Norethindrone is also bound to SHBG and albumin in the plasma (about 90%).

2. Pharmacokinetics:

a) Single and Multiple Dose

The single dose pharmacokinetics of estradiol and NETA following administration of ALIATIS® (50/250) patch were evaluated in studies 122 and 126. Multiple dose/steady state pharmacokinetics were evaluated in study 104. All studies were conducted in healthy postmenopausal women. The results are listed in Table VIII. Figure 2 presents concentration over time profiles for estradiol and NETA following a single application of Aliatis® (50/250) transdermal system.

Table VIII. Summary of pharmacokinetic parameters (mean \pm SD), for estradiol and norethindrone after single and multiple dose applications of Aliatis™ to the lower abdomen

Parameter	Study 122 Single Dose (4 Days)	Study 126 Single Dose (4 Days)	Study 104 Multiple dose (3X3.5 Days)
Estradiol (uncorrected for baseline)			
C _{max} (pg/mL)	81.0 (31.4)	74.7 (22.8)	70.6 (30.0)
C _{avg} (pg/mL)	-	-	50.3(21.0)
AUC ₀₋₁₃₂ (pg.hr/mL)	5720 (1956)	5108 (1727)	-
AUC _{ss(168-252)} (pg.hr/mL)	-	-	4224 (1761)
Norethindrone			
C _{max} (pg/mL)	927 (387)	873 (541)	1060 (543)
C _{avg} (pg/mL)	-	-	839.8(414)
AUC ₀₋₁₃₂ (pg.hr/mL)	54 (11.8)	55 (27.3)	192 (17.3)
AUC _{ss(168-252)} (pg.hr/mL)	78294 (35389)	64742 (43701)	-

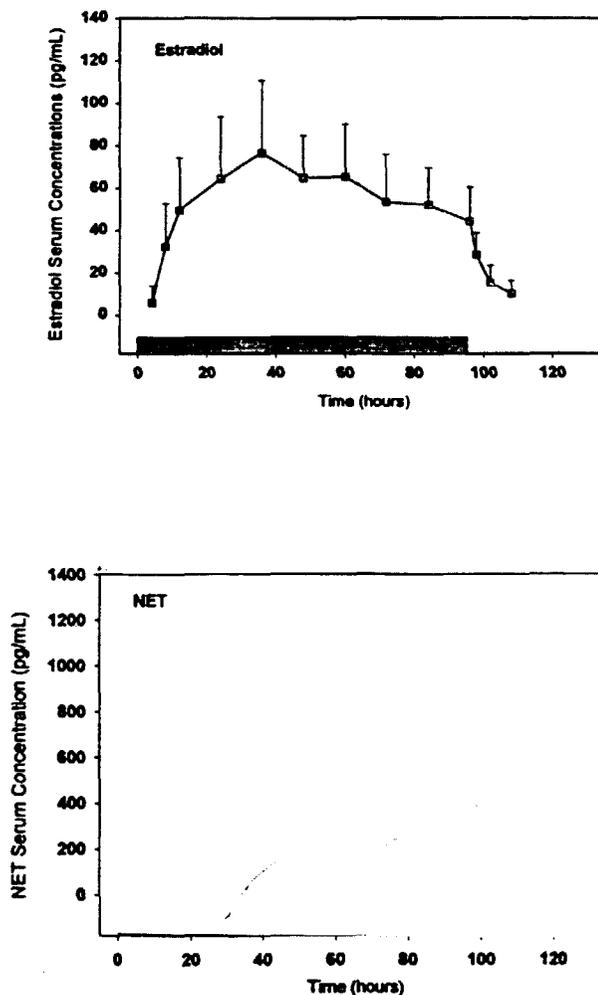


Figure 2. Mean (SD) Estradiol (top) and NET (bottom) serum concentrations following application of a single Aliatis® patch (50/250).

Reviewer Comments:

1. Steady state levels were achieved for estradiol and NET 12-24 hours following a single application of Aliatis® transdermal system.
2. Multiple dosing of Aliatis® transdermal system resulted in no accumulation of estradiol or NET.

3. Bioavailability/Bioequivalence:

a) Absolute/Relative Bioavailability

The absolute bioavailability of estradiol and NETA was not determined for this NDA. The relative bioavailability of Aliatis® patches and the marketed product Menorest® was evaluated in 40 postmenopausal women after three consecutive patches (three consecutive 3.5 day periods) in Study 104. The results are listed in Table IX. Additionally, the relative bioavailability of Aliatis™ patches was determined following a single 4 day application to different body sites: abdomen versus buttocks, in 18 postmenopausal women. The results are listed in Table X.

Table IX. Mean estradiol (uncorrected for base line) pharmacokinetic parameters and relative bioavailability of Aliatis™ patches and Menorest® 50 at steady state following application to the lower abdomen.

Parameter	Aliatis™ patch (50/140)	Aliatis™ patch (50/250)	Menorest® 50
AUC ₀₋₂₅₂ (pg.hr/mL)	3792	4224	4302
C _{max} (pg/mL)	71.1	70.6	71.4
C ₁₂ (pg/mL)	45.1	50.3	51.2
Bioavailability relative to Menorest® (%F)	88.1	98.2	-

Table X. Mean (SD) pharmacokinetic parameter estimates for estradiol (uncorrected for baseline) and norethindrone following the application of Aliatis® (50/250) patch to the lower abdomen and buttocks.

Parameters	50/250 Abdomen	50/250 Buttock	Abd/But Ratio %	90% CI
ESTRADIOL				
AUC ₀₋₁₃₂ (pg.hr/mL)	5720.3 (1956)	4612.2 (1407)	122.1	109.1-136.6
C _{max} (pg/mL)	81.0 (31.3)	65.6 (22.0)	121.5	121.5-141.7
T _{max} (hr)	48.7 (21.6)	50.0 (18.5)	-	-
NORETHINDRONE				
AUC ₀₋₁₃₂ (pg.hr/mL)	78294 (35389)	60916 (18214)	122.3	110.6-136.2
C _{max} (pg/mL)	927 (386)	774 (245)	115.9	107.8-124.7
T _{max} (hr)	54.0(11.8)	52.9 (22.7)	-	-

Reviewer Comments:

1. The bioavailability of estradiol in Aliatis™ patch 50/250 appears to be the same as that of Menorest® 50 patch. The bioavailability of Aliatis™ 50/140 patch is about 88% relative to the Menorest® 50 patch.
2. Bioavailability is 24% and 28% greater for estradiol and NETA, respectively, when the patch is applied to the abdomen (compared to the buttocks).

b) Bioequivalence,

No studies were needed to demonstrate bioequivalence between the clinically tested patches and the to be marketed patches because they are the same. Bioequivalence of the estradiol component of Aliatis™ patches was evaluated using Menorest® patch as a reference product. The results are listed in Table XI.

Table XI. 90% Confidence Intervals (CI) and LS Mean Ratios for the Test Mean versus the Reference Mean for the following treatments:

A: Aliatis™ 50/140; B: Aliatis™ 50/250; C: Menorest® 50.

Treatment	PK Parameter N=40	LS Mean Ratio (%)	Lower CI (%)	Upper CI (%)
A:C	E ₇ AUC	83.0	75.9	90.8
B:C	E ₇ AUC	97.9	89.6	106.9
A:C	E ₇ C _{max}	98.7	90.6	107.6
B:C	E ₇ C _{max}	100.4	92.2	109.4

Reviewer Comments:

1. The estradiol component of Aliatis® patch (50/250) was bioequivalent to that of the Menorest® patch.
2. The estradiol component of Aliatis® patch (50/140) was bioequivalent to Menorest® with regard to C_{max} but not AUC. The 90% CI indicate that the extent of absorption of estradiol is lower when compared to Menorest®. According to Dr. Phil Price (HFD-580), this difference in the extent of absorption is not clinically significant for the treatment of vasomotor symptoms, but can be significant for other indications (i.e., osteoporosis).

c) Dose Proportionality

Dose proportionality studies comparing the NETA pharmacokinetics of Aliatis® patches (50/140) and (50/250) were conducted in Study 104. The results are listed in Table XVII. The dose of the estradiol component is the same in both patches, therefore, dose proportionality studies for estradiol are not needed. It should be noted, however, that the 50/140 system does not deliver the same amount of E2 *in vitro* as the 50/250 system, and this is also reflected *in vivo*.

Reviewer Comments:

1. Dose proportionality was demonstrated for NETA in Aliatis® patches (50/140) and (50/250).

4. Estimation of Delivery Rate

Delivery rate was estimated by measuring the residual amount of estradiol and NETA in the patches following application to postmenopausal women over 96 hours. This method is appropriate because the total amount of estradiol and NETA delivered is > 20% of the amount of estradiol and NETA in unused patches. The percent difference between the nominal and the mean measured concentration ranged from -6.9% and -2.35% for estradiol and -4.72% and 0.12% for NETA.

5. Special Populations

No studies were performed in Special Populations.

6. Metabolism

The metabolism of estradiol and NETA is well defined and no new studies were needed.

7. Drug Interactions

No studies were done to evaluate drug interactions.

8. PK/PD Relationships and Population Pharmacokinetics

No studies were done to examine PK/PD relationships. Population PK, using data from clinical studies, were evaluated using a linear regression model: AUC was predicted from one or two steady state data points per patient. This approach was used because the sparsity of data precluded a meaningful analysis with NONMEM.

Reviewer Comments:

1. The population PK analysis and validation are acceptable.
2. Overall, the results of the population analysis were in agreement with data obtained in previous PK studies which used more frequent sampling and generated more complete PK profiles.

VIII. Adhesion

Patch adherence of Aliatis[®] transdermal systems (50/140) and (50/250) was evaluated using 38 systems. Of this total, 2 patches were replaced (one fell off, the other was too wrinkled), 34 (89%) had greater than 90% adherence (completely on), and 2 had 75-90% adherence ("edges lifting off"). Adhesion data from clinical trials (total of 1287 patients

treated) showed that Aliatis® patches adhered to skin nearly 90% of the time over the 3 to 4 day wear period. Less than 2% of the patients required re-application or replacement of the system.

Reviewer Comments:

1. Aliatis® patches (50/140) and (50/250) do not appear to have problems with adherence.

IX. Labeling

The sponsor's proposed labeling is included in Attachment A.

Reviewer comment:

The recommended labeling changes are based in part on the Division's (DRUDP) draft guidance for estrogen labeling. The changes are listed below:

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pages of trade

secret and/or

confidential

commercial

information

Attachment A

NDA 20-870

Proposed Labeling

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Attachment B

NDA 20-870

Study Summaries

PROTOCOL: RPR 106522D-104

Title of the study: A Steady-State Bioavailability Study Of The RPR Estradiol/Norethisterone Acetate (Neta) Transdermal System At Three Dose Levels (50/100, 50/250, 50/400) And RPR Menorest® 50

Study period: Clinical Phase: I

- Objectives:**
- A. To determine, via timed serum sampling, the steady-state pharmacokinetic profiles of estradiol, estrone and NET prior to, during and for 48 hours following three consecutive 84-hour patch applications of RPR estradiol/NETA 50/100, 50/250, 50/400 and Menorest® 50.
 - B. To estimate the bioavailability of estradiol among products with varying NETA concentrations.
 - C. To assess estradiol relative bioavailability with the 3 RPR estradiol/NETA patches vs. Menorest® 50.
 - D. To evaluate NETA dose proportionality among three estradiol/NETA products at fixed estradiol doses.
 - E. To evaluate clinical safety and skin adherence and tolerability.

Methodology: Open-label, randomized, 4-way cross-over, complete block design

Number of subjects (total and for each treatment):

TOTAL: Enrolled: 40

Discontinued: 0

Completed Study: 40

Diagnosis and Main Criteria for Inclusion:

1. Post-menopausal Caucasian women aged 40-70 years who were judged by the Investigator to be healthy on the basis of pre-study physical examination, Pap smear, 12 lead electrocardiogram, and screening laboratory tests: full set of hematology and blood chemistry tests, urinalysis, addictive drug screen and Human Immuno-deficiency Virus (HIV) and hepatitis B serology.
2. Menopausal status based on the absence of menses for at least one year's duration, vaginal examination consistent with menopausal status, baseline serum estradiol levels ≤ 20 pg/ml, and FSH levels > 40 IU/L.

Test product, dose and mode of administration, batch No.: 50 μ g 17 β estradiol/140 μ g NETA (Lot # 9411440), 50 μ g 17 β estradiol/250 μ g NETA (Lot # 9411441) and 50 μ g 17 β estradiol/400 μ g NETA (Lot # 9411442) /Patch/Transdermal

Duration of treatment: 10.5 days for each treatment

Reference therapy, dose and mode of administration, batch No.: Menorest® 50 Transdermal/Patch/50 μ g 17 β estradiol (Lot #9408291)

Menorest® is marketed in Europe and elsewhere by RPR and by Novartis in North America as Vivelle™.

Criteria for evaluation: Safety : adverse event recording, vital signs, routine laboratory tests.

Pharmacokinetics : The biopharmaceutic parameters for NET, estrone, and estradiol were calculated using noncompartmental techniques. The maximum serum concentrations (C_{max}) and the times to reach C_{max} (T_{max}) at steady-state were determined directly from the observed serum concentration-time profiles over the 168 hr to 252 hr sampling interval. The area under the serum concentration-time curves at steady-state were calculated by linear trapezoidal summation over the sampling interval (168 hrs to 252 hrs).

Analytical methods:

Statistical methodology:

Pharmacokinetics: Statistical analysis of the biopharmaceutic parameters for the RPR estradiol/NETA patches (50/140, 50/250 and 50/400) and for RPR Menorest® 50 was performed using the General Linear

Models (PROC GLM) procedure within SAS version 6.10 (SAS Institute, Cary, NC). An analysis of variance (ANOVA) was used to test the differences in the dose-normalized mean NET biopharmaceutic parameters between the reference treatment, RPR 50/250 estradiol/NETA patch, and the 50/140 and 50/400 RPR estradiol/NETA patches. An ANOVA was also used to test the differences in mean estradiol and estrone biopharmaceutic parameters between the reference treatment, RPR Menorest® 50, and the 50/140, 50/250, and 50/400 RPR estradiol/NETA patches. The statistical models tested for the effects of treatment, period, group, subject within group, and subject at the significance level of 0.05. The biopharmaceutic parameters, AUC_{0-252} and C_{max} were analyzed statistically on the untransformed and ln transformed data. Statistical comparisons of T_{max} were made on the untransformed data. A univariate procedure (PROC UNIVARIATE) was used to assess the normality and to test for outliers in the studentized residuals from PROC GLM. Ninety percent confidence intervals were constructed for the least squares mean of the ln transformed data for the dose normalized parameters, AUC_{0-252} and C_{max} , for norethindrone, and for AUC_{0-252} and C_{max} for estradiol and estrone.

Pharmacokinetic Results: The pharmacokinetic analysis indicated that the RPR 50/140 patch delivers lower serum estradiol concentrations and that the RPR 50/400 patch delivers higher serum estradiol concentrations when compared to the RPR 50/250 patch.

The RPR 50/250 patch demonstrated equivalent estradiol bioavailability when compared to the RPR Menorest® 50 patch, whereas the RPR 50/140 and 50/400 patches and the RPR Menorest® 50 patches were not equivalent

The rate and extent of norethindrone delivery was dose proportional for the RPR 50/140, 50/250, and 50/400 patches.

Mean (%CV) biopharmaceutic parameter estimates for NET following the application of the 50/140, 50/250, 50/400 RPR estradiol/NETA patches are presented below.

	Parameters	50/140 RPR patch	50/250 RPR patch	50/400 RPR patch
NET (Excluding Subject 50/140 and 50/400, Subject 50/140)	AUC_{0-252} (pg*hr/mL)	41057 (50.1)	70541 (49.3)	117240 (44.9)
	C_{max} (pg/mL)	617.2 (55.2)	1059.9 (51.2)	1742.5 (48.0)
	C_{min} (pg/mL)	385.8 (35.4)	686.4 (44.6)	1184 (51.0)
	C_{ave} (pg/mL)	488.8 (50.1)	839.8 (49.3)	1395.7 (44.9)
	T_{max} (hr)	193.3 (11.5)	192.1 (9.0)	194.0 (10.8)

Statistical comparisons between treatments for norethindrone (dose-normalized, ln transformed parameters) are presented below.

Parameter	Comparison	p-value
AUC_{0-252}	RPR 50/140 vs RPR 50/250	0.3010
C_{max}	RPR 50/140 vs RPR 50/250	0.4912
T_{max}	RPR 50/140 vs RPR 50/250	0.6445
AUC_{0-252}	RPR 50/400 vs RPR 50/250	0.1745
C_{max}	RPR 50/400 vs RPR 50/250	0.3956
T_{max}	RPR 50/400 vs RPR 50/250	0.3345

90% Confidence Intervals (CI) and LS Mean Ratios for the Test Mean versus the Reference Mean for the following treatments: A: RPR estradiol/NETA 50/140, B: RPR estradiol/NETA 50/250, C: RPR estradiol/NETA 50/400

	Parameter	Lower CI (%)	LS Mean Ratio (%)	Upper CI (%)
NET (ln transformed)	AUC (A:B)	96.9	105.3	114.4
	AUC (C:B)	98.5	107.1	116.3
	Cmax (A:B)	94.7	103.9	114.0
	Cmax (C:B)	95.6	104.8	114.9

Mean (%CV) biopharmaceutic parameter estimates for estradiol following the application of the 50/140, 50/250, 50/400 RPR estradiol/NETA patches and the RPR Menorest® 50 patch are presented below.

	Parameters	50/140	50/250	50/400	Menorest® 50
Estradiol (Excluding Sub 50/140)	AUC ₀₋₂₄ (168-252) (pg*hr/mL)	3792.1 (46.0)	4224.1 (41.7)	5179.5 (40.5)	4301.5 (37.8)
	Cmax (pg/mL)	71.1 (45.6)	70.6 (42.5)	89.9 (51.0)	71.4 (46.4)
	Cmin (pg/mL)	26.7 (64.4)	36.9 (47.8)	47.6 (50.8)	37.1 (26.2)
	Cave (pg/mL)	45.1 (46.0)	50.3 (41.7)	61.7 (40.5)	51.2 (37.8)
	Tmax (hr)	189.5 (9.4)	191.3 (10.0)	195.1 (10.6)	191.4 (10.7)
	Absolute Fluctuation	45.3 (65.5)	32.3 (75.5)	39.9 (86.5)	34.3 (85.0)
	Relative Fluctuation	1.06 (64.1)	0.62 (66.0)	0.59 (66.6)	0.58 (62.8)

Statistical comparisons between treatments for estradiol (ln transformed parameters) are presented below.

Parameter	Comparison	p-value
AUC ₀₋₂₄ (168-252)	RPR 50/140 vs RPR 50/250	0.0031*
Cmax	RPR 50/140 vs RPR 50/250	0.7403
Tmax	RPR 50/140 vs RPR 50/250	0.7629
AUC ₀₋₂₄ (168-252)	RPR 50/400 vs RPR 50/250	0.0003*
Cmax	RPR 50/400 vs RPR 50/250	0.0001*
Tmax	RPR 50/400 vs RPR 50/250	0.2916

*significant

Statistical comparisons between treatments for estradiol (ln transformed parameters) with Menorest® 50 as the reference treatment

Parameter	Comparison	p-value
AUC ₀₋₂₄ (168-252)	RPR 50/140 vs Menorest®	0.0008*
Cmax	RPR 50/140 vs Menorest®	0.8033
Tmax	RPR 50/140 vs Menorest®	0.7697
AUC ₀₋₂₄ (168-252)	RPR 50/250 vs Menorest®	0.6860
Cmax	RPR 50/250 vs Menorest®	0.9337
Tmax	RPR 50/250 vs Menorest®	0.9928
AUC ₀₋₂₄ (168-252)	RPR 50/400 vs Menorest®	0.0010*
Cmax	RPR 50/400 vs Menorest®	0.0001*
Tmax	RPR 50/400 vs Menorest®	0.2875

*significant

90% Confidence Intervals (CI) and LS Mean Ratios for the Test Mean versus the Reference Mean for the following treatments: A: RPR estradiol/NETA 50/140, B: RPR estradiol/NETA 50/250, C: RPR estradiol/NETA 50/400, D: RPR Menorest® 50

	Parameter	Lower CI (%)	LS Mean Ratio (%)	Upper CI (%)
Estradiol (ln transformed)	AUC (A:D)	75.9	83.0	90.8
	AUC (B:D)	89.6	97.9	106.9
	AUC (C:D)	109.7	119.8	131.0
	Cmax (A:D)	90.6	98.7	107.6
	Cmax (B:D)	92.2	100.4	109.4
	Cmax (C:D)	113.0	123.0	134.0

Mean (%CV) biopharmaceutic parameter estimates for estrone following the application of the 50/140, 50/250, 50/400 RPR estradiol/NETA patches and the RPR Menorest® 50 patch are presented below.

	Parameters	50/140	50/250	50/400	Menorest® 50
Estrone (Excluding Subject 50/140 and Subject 50/250)	AUC ₀₋₂₄ (168-252) (pg*hr/mL)	4491.5 (34.9)	5050.1 (30.0)	5218.1 (35.0)	4729.5 (33.9)
	Cmax (pg/mL)	71.9 (31.7)	78.4 (28.7)	82.1 (39.3)	71.8 (29.2)
	Cmin (pg/mL)	48.5 (39.2)	57.8 (37.4)	59.1 (35.6)	53.1 (35.0)
	Cave (pg/mL)	53.5 (34.9)	60.1 (30.0)	62.1 (35.0)	56.3 (33.9)
	Tmax (hr)	211.5 (15.8)	214.7 (15.5)	203.5 (14.1)	206.4 (14.6)
	Absolute Fluctuation	23.3 (84.5)	20.7 (92.6)	23.1 (107.1)	18.7 (79.6)
	Relative Fluctuation	0.45 (97.0)	0.35 (89.6)	0.34 (85.3)	0.35 (74.5)

Statistical comparisons between treatments for estrone (ln transformed parameters) are presented below.

Parameter	Comparison	p-value
AUC ₀₋₂₄ (168-252)	RPR 50/140 vs Menorest®	0.1374
Cmax	RPR 50/140 vs Menorest®	0.8432
Tmax	RPR 50/140 vs Menorest®	0.3955
AUC ₀₋₂₄ (168-252)	RPR 50/250 vs Menorest®	0.0645
Cmax	RPR 50/250 vs Menorest®	0.0524
Tmax	RPR 50/250 vs Menorest®	0.2290
AUC ₀₋₂₄ (168-252)	RPR 50/400 vs Menorest®	0.0197*
Cmax	RPR 50/400 vs Menorest®	0.0098*
Tmax	RPR 50/400 vs Menorest®	0.6600

*significant

90% Confidence Intervals (CI) and LS Mean Ratios for the Test Mean versus the Reference Mean for the following treatments: A: RPR estradiol/NETA 50/140, B: RPR estradiol/NETA 50/250, C: RPR estradiol/NETA 50/400, D: RPR Menorest® 50

	Parameter	Lower CI (%)	LS Mean Ratio (%)	Upper CI (%)
Estrone (ln transformed)	AUC (A:D)	87.6	93.9	100.7
	AUC (B:D)	100.9	108.3	116.2
	AUC (C:D)	103.0	110.3	118.1
	Cmax (A:D)	92.7	99.2	106.1
	Cmax (B:D)	101.3	108.4	116.1
	Cmax (C:D)	104.0	111.2	118.9

- **Conclusions:** Steady-state serum NET, estradiol, and estrone concentrations are achieved by the third patch application period. Multiple patch administrations (3 consecutive 3.5 day wear periods) resulted in the delivery of constant serum concentrations of NET, estradiol, and estrone at steady-state.
- An analysis of variance demonstrated statistically significant differences between the RPR 50/250 patch and the RPR 50/140 and 50/400 patches for AUC₀₋₂₄(168-252) indicating that the RPR 50/140 patch delivers lower serum estradiol concentrations and that the RPR 50/400 patch delivers higher serum estradiol concentrations as compared to the RPR 50/250 patch. Significantly higher Cmax estimates were also seen for the RPR 50/400 patch as compared to the RPR 50/250 patch. Significant differences were not seen when comparing Cmax estimates for the RPR 50/140 vs 50/250 patches, and Tmax estimates were not different for any of the RPR patches.
- The RPR 50/250 estradiol/NETA patch demonstrated equivalent estradiol bioavailability when compared to the RPR Menorest® 50 patch as evidenced by bioequivalent AUC₀₋₂₄(168-252) and Cmax estimates. The RPR 50/400 patches and the RPR Menorest® 50 patches were not bioequivalent, with differences indicating that the RPR 50/400 patch delivers greater estradiol concentrations as compared to the RPR Menorest® 50 patch. The RPR 50/140 patch was bioequivalent to the RPR Menorest® 50 patch in terms of Cmax, but was bioinequivalent in terms of AUC₀₋₂₄(168-252), suggesting equivalent rates of absorption and but inequivalent extents of absorption of estradiol from these patches.
- The AUC₀₋₂₄(168-252) and Cmax estimates for norethindrone are dose proportional for the RPR 50/140, 50/250, and 50/400 estradiol/NETA patches.

Reviewer Comments:

Reviewer agrees with sponsor's conclusions.

PROTOCOL : RPR 106522D-122

Title of the study: A Phase I, Open-Label, Randomized, 2-Way Crossover, Relative Bioavailability Study of RPR Adhesive-Based Transdermal Estradiol/NETA Patch (50/250) Comparing Abdomen Versus Buttock Placement in Healthy Postmenopausal Women

Study period: Clinical Phase: I

Start (Date first subject randomized): 17-Oct-95

End (Last subject discharge date): 5-Nov-95

Objectives:

- A. To compare, via timed serum sampling, the pharmacokinetic (PK) profiles of estradiol, estrone, and NET prior to, during, and for 36 hours following single 4 day patch applications of transdermal estradiol/NETA (50/250) patches in an abdomen versus buttock placement,
- B. To assess the relative bioavailability of these 2 placements

Methodology: Open-label, randomized, 2-way cross-over, complete block design

Number of subjects (total and for each treatment):

TOTAL: Enrolled: 18:

Discontinued: 0:

Completed Study: 18:

Diagnosis and Main Criteria for Inclusion:

1. Postmenopausal Caucasian women aged 40-70 years who were judged by the Investigator to be healthy on the basis of prestudy physical examination, Pap smear, 12 lead electrocardiogram, and screening laboratory tests, including a full set of hematology and blood chemistry tests, urinalysis, addictive drug screen, human immunodeficiency virus (HIV) and hepatitis B serology.
2. Menopausal status was to be based on the absence of menses of at least one year's duration, vaginal examination consistent with menopausal status, baseline serum estradiol levels ≤ 20 pg/ml, and FSH levels > 50 IU/L.

Test product, dose and mode of administration, batch No.: 50 μ g 17 β estradiol/250 μ g NETA (Lot # 9503636)

Duration of treatment: 8 days

Criteria for evaluation: Safety : adverse event recording, vital signs, routine laboratory tests

Pharmacokinetics : The biopharmaceutic parameters for NET, estrone, and estradiol were calculated using noncompartmental techniques. The maximum serum concentrations (C_{max}) and the times to reach C_{max} (T_{max}) at steady-state were determined directly from the observed serum concentration-time profiles over the 132 hr sampling interval. The area under the serum concentration-time curves at steady-state were calculated by linear trapezoidal summation over the sampling interval (predose to 132 hrs).

Analytical methods:

Pharmacokinetics : Statistical analysis of the biopharmaceutic parameters for the RPR estradiol/NETA patch (50/250 patch, abdomen versus buttock placement) was performed using the General Linear Models (PROC GLM) procedure within SAS version 6.10 (SAS Institute, Cary, NC). An analysis of variance (ANOVA) was used to test the differences in the mean NET, estradiol, and estrone biopharmaceutic parameters between the two patch placement locations (abdomen versus buttock). The statistical models tested for the effects of treatment (patch placement), period, group, subject within group, and subject at the

significance level of 0.05. The biopharmaceutic parameters, AUC (0-132) and Cmax were analyzed statistically on the untransformed and ln transformed data. Statistical comparisons of Tmax were made on the untransformed data. A univariate procedure (PROC UNIVARIATE) was used to assess the normality and to test for outliers in the studentized residuals from PROC GLM. Ninety percent confidence intervals were constructed for the least squares mean of the ln transformed data for the AUC (0-132) and Cmax, for NET, estradiol and estrone.

Pharmacokinetic Results: The pharmacokinetic analysis demonstrated that the rates (Cmax) and extents (AUC) of NET and estradiol absorption were greater following the application of the RPR 50/250 patch on the abdomen as compared to the buttocks. These results indicate that the RPR 50/250 patch delivers approximately 28% more NET and approximately 24% more estradiol when placed on the abdomen than when placed on the buttocks. Differences were not seen for estrone Cmax and AUC when comparing the different patch placements.

Mean (%CV) biopharmaceutic parameter estimates for NET following the application of the RPR 50/250 patch on the abdomen and buttock

	Parameters	50/250 Abdomen	50/250 Buttock	Ratio (Abdomen/Buttock)
Norethindrone	AUC (0-132) (pg*hr/mL)	78294 (45.2)	60916 (29.9)	1.28
	Cmax (pg/mL)	927 (41.6)	774.3 (31.7)	1.19
	Tmax (hr)	54 (21.9)	52.9 (42.9)	

Statistical comparisons between patch placements for the ln transformed norethindrone parameters

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.0030*
Cmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.0027*
Tmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.3120

*significant

Mean (%CV) biopharmaceutic parameter estimates for estradiol following the application of the RPR 50/250 patch on the abdomen and buttock

	Parameters	50/250 Abdomen	50/250 Buttock	Ratio (Abdomen/Buttock)
Estradiol	AUC (0-132) (pg*hr/mL)	5720.3 (34.2)	4612.2 (30.5)	1.24
	Cmax (pg/mL)	81.0 (38.7)	65.6 (33.6)	1.23
	Tmax (hr)	48.7 (44.3)	50.0 (37.0)	

Statistical comparisons between patch placements for the ln transformed estradiol parameters

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.0068*
Cmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.0428*
Tmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.6550 ^{ns}

*significant

Mean (%CV) biopharmaceutic parameter estimates for estrone following the application of the RPR 50/250 patch on the abdomen and buttock

	Parameters	50/250 Abdomen	50/250 Buttock	Ratio (Abdomen/Buttock)
Estrone	AUC(0-132) (pg*hr/mL)	8050.2 (34.5)	7954.6 (32.9)	1.01 ^{ns}
	Cmax (pg/mL)	91.3 (34.5)	89.2 (34.6)	1.02
	Tmax (hr)	63.8 (39.5)	62.4 (42.2)	

Statistical comparisons between patch placements for the ln transformed estrone parameters

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.9023
Cmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.6093
Tmax	RPR 50/250 Abdomen vs RPR 50/250 Buttock	0.9414

Conclusions:

- The AUC and Cmax estimates were 28% greater for NET and 24% greater for estradiol following the application of the RPR 50/250 patch on the abdomen as compared to the buttocks. This indicates that the RPR 50/250 patch delivers more NET and estradiol when placed on the abdomen than when placed on the buttocks.
- Similar AUC and Cmax estimates were seen for estrone following either patch placement.

Reviewer Comment:

Reviewer is in agreement with sponsor's conclusions.

PROTOCOL NUMBER: 106522D-126

Title of the Study: A phase 1, open randomized, 3-way crossover study of the relative bioavailability of two formulations of RPR adhesive-based transdermal estradiol/NETA patch at two dose levels (50/100, 50/250) and Estragest® in healthy postmenopausal women:

Study Period: Clinical Phase : I

Start: 13 July 1996

End: 27 August 1996:

Objectives :

- To determine, via timed serum sampling, the pharmacokinetic profiles of estradiol, estrone and NETA prior to, during and for 36 hours following a 96 hour patch application of RPR 106522 (50/100, 50/250) and Estragest®.
- To assess estradiol and NETA relative bioavailability with the 2 different RPR 106522 patches versus Estragest®.

Methodology : Open, randomized, three-way cross-over study comprising three periods with single patch applications. A wash-out period of at least 7 days elapsed between removal of a patch and application of the next one.

Number of subjects/patients (total and for each treatment):

Enrolled : 18

Discontinued : 0

Completed Study : 18

Diagnosis and Main Criteria for Inclusion : Healthy post-menopausal women aged 40 to 70 years.

Test product, dose and mode of administration, Batch number :

RPR 106522, 50/140* (0.050 mg 17β estradiol and 0.140 mg NETA)

RPR 106522, 50/250 (0.050 mg 17β estradiol and 0.250 mg NETA)

Single patch application, transdermal route.

Batch : CB 06355 (50/140)/ Lot No. 9411440

Batch: CB 06339 (50/250)/Lot No. 9411441

*The size of the original RPR 106522 50/100 patch was increased from 6.5 cm² to 9 cm² to optimize the delivery of estradiol to 50 mcg/day thereby resulting in a delivery of 140 mcg/day of NET.

Duration of treatment : 96 hours for each period of the study

Reference therapy, dose and mode of administration, Batch number : Estragest® 50/250 (0.050 mg 17β estradiol and 0.250 mg NETA)

Single patch application, transdermal route.

Batch : B 042200

Pharmacokinetics : The biopharmaceutic parameters for NET, estrone and estradiol were calculated using noncompartmental techniques. The maximum serum concentrations (C_{max}), and the times to reach C_{max} (T_{max}) at steady state were determined directly from the observed serum concentration-time profiles over the 132 hr sampling interval. The area under the serum concentration-times curves at steady-state were calculated by linear trapezoidal summation over the sampling interval (predose to 132 hrs).

Analytical methods:

Statistical methodology:

Pharmacokinetics :

All pharmacokinetic analyses were carried out using SAS procedures. Comparisons were performed on the pharmacokinetic parameters using an analysis of variance and tested for the effects of subject, subject within sequence, sequence, period and treatment at a significance level of 0.05.

Pharmacokinetic results : An analysis of variance was performed to compare the bioavailability of NET and estradiol following the RPR estradiol/NETA 50/140 and 50/250 patches and Estragest® 50/250. Significant differences were not seen when comparing the NET AUC estimates and indicate that, although the profiles for NET from the RPR 106522 50/250 and Estragest® patches are very different, the exposures to NET are similar. Significant differences were seen, however, for Cmax and indicate that the Estragest® patch provides higher maximum serum NET concentrations as compared to the RPR 106522 50/250 patch.

The estimates for estradiol AUC and Cmax for the RPR 106522 50/250 patch and Estragest® were comparable. Significant differences were seen for AUC when comparing the RPR 106522 50/140 patch to Estragest®. Cmax estimates, however, were not different for the RPR 106522 50/140 patch and Estragest®. Significant differences were also seen for estradiol AUC and Cmax when comparing the RPR 106522 50/140 patch to the RPR 106522 50/250 patch.

Mean (%CV) pharmacokinetic parameters for NET following the application of the RPR 106522 50/140 patch, the RPR 106522 50/250 patch, and Estragest® for 4 days

	Parameters	RPR 50/140	RPR 50/250	Estragest® 50/250
NET	AUC (0-132) (pg*hr/mL)	36657 (62.2)	64742 (67.5)	62887 (45.5)
	Cmax (pg/mL)	431.5 (56.8)	872.9 (62.0)	1041.5 (42.7)
	Tmax (hr)	67.1 (43.4)	55.0 (49.7)	89.4 (5.3)

Statistical comparisons between treatments for the NET pharmacokinetic parameters

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 vs Estragest®	0.4237
Cmax	RPR 50/250 vs Estragest®	0.0012*

*significant

Mean (%CV) pharmacokinetic parameters for estradiol following the application of the RPR 106522 50/140 patch, the RPR 106522 50/250 patch, and Estragest® for 4 days

	Parameters	RPR 50/140	RPR 50/250	Estragest® 50/250
Estradiol	AUC (0-132) (pg*hr/mL)	3292.4 (45.5)	5108.2 (33.8)	4082.4 (20.4)
	Cmax (pg/mL)	62.0 (43.7)	74.7 (30.7)	62.6 (29.6)
	Tmax (hr)	26.7 (24.7)	52 (55.8)	75.7 (25.1)

Statistical comparisons between treatments for estradiol

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 vs Estragest®	0.1056
AUC(0-132)	RPR 50/140 vs Estragest®	0.0113*
AUC(0-132)	RPR 50/250 vs RPR 50/140	0.0001*
Cmax	RPR 50/250 vs Estragest®	0.0559
Cmax	RPR 50/140 vs Estragest®	0.5419
Cmax	RPR 50/250 vs RPR 50/140	0.0140*

*significant

Mean (%CV) pharmacokinetic parameters for estrone following the application of the RPR 106522 50/140 patch, the RPR 106522 50/250 patch, and Estragest® for 4 days

	Parameters	RPR 50/140	RPR 50/250	Estragest® 50/250
Estrone	AUC (0-132) (pg*hr/mL)	6221.6 (32.3)	6951 (28.1)	6427.5 (32.7)
	Cmax (pg/mL)	73.0 (19.3)	79.6 (26.9)	70.9 (31.5)
	Tmax (hr)	35 (71.6)	55.3 (64.0)	80.7 (40.4)

Statistical comparisons between treatments for estrone

Parameter	Comparison	p-value
AUC(0-132)	RPR 50/250 vs Estragest®	0.0739
AUC(0-132)	RPR 50/140 vs Estragest®	0.4578
AUC(0-132)	RPR 50/250 vs RPR 50/140	0.0142*
Cmax	RPR 50/250 vs Estragest®	0.0329*
Cmax	RPR 50/140 vs Estragest®	0.2857
Cmax	RPR 50/250 vs RPR 50/140	0.2612

Conclusions :

- The RPR estradiol/NETA patches and Estragest® produce different pharmacokinetic profiles for NET. The data suggest that the RPR patches produce steady-state NET serum concentrations over the patch wear period which decline after the patch is removed, whereas the NET profiles following Estragest® continually increase to peak concentrations and decline following patch removal. The differences between patches for estradiol and estrone profiles are not as pronounced.
- The AUC estimates for NET following the RPR estradiol/NETA 50/250 patch and Estragest® are similar. Cmax estimates, however, are different and indicate that the Estragest® patch provides higher maximum serum NET concentrations as compared to the RPR 106522 50/250 patch. The AUC and Cmax estimates for estradiol for the RPR 106522 50/250 patch and Estragest® were comparable indicating similar estradiol bioavailabilities for both patches. Although the maximum estradiol serum concentrations for the RPR 106522 50/140 patch and Estragest® were comparable, the AUC estimates indicate that the RPR 106522 50/140 patch delivers less estradiol when compared to Estragest®. The bioavailability of estradiol following the application of the RPR 106522 50/140 and RPR 106522 50/250 patches is different; that is, the RPR 106522 50/140 patch delivers less estradiol than the RPR 106522 50/250 patch.

Reviewer Comment:

Reviewer is in agreement with sponsor's conclusions.