CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-527/S-017

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OCT - 3 2000

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**20-527 SLR-017**
To:	**HFD-580**
Place:	PKLN 17B43
Compound:	0.45 or 0.3 mg conjugated estrogens and 1.5 mg medroxyprogesterone acetate
Sponsor:	Wyeth-Ayerst Research
Date:	August 1, 2000, 12:00 noon
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

NDA 20-527 SLR-017 ([redacted] for 0.45 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA) or 0.3 mg CE/1.5 mg MPA oral tablets in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy was submitted on June 15, 2000. This sNDA concerns the low dose CE and MPA tablets, which support the low-dose Health and Osteoporosis, Progestin and Estrogen (HOPE) study of CE and MPA. Sponsor also submitted NDA 04-782 SE2-115 for 0.45 mg CE alone tablet on July 31, 2000 for the same indications. PREMARIN® is available as 0.3, 0.625, 0.9, 1.25, and 2.5 mg CE alone oral tablets. PREMPRO™ is available as 0.625 mg CE/2.5 mg MPA or 0.625mg CE/5 mg MPA oral tablets. PREMARIN® is derived from pregnant mares' urine, which contains more than 10 estrogens, including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone. MPA is a synthetic progestin derived from 17α-hydroxyprogesterone.

Comments:

1. Sponsor conducted 2 studies (0713D2-119-US and 0713D2-120-US) to support the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017 (see Attachment). These 2 studies are identical in design except different combination strengths of CE and MPA were administered. Study 0713D2-119-US also supports the recently submitted NDA 04-782 SE2-115.
2. 0713D2-119-US was a randomized, single-dose, 4-period/treatment, crossover study that assessed the relative bioavailability (BA) of estrogens and MPA from 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE alone oral tablets.
3. 0713D2-120-US was a randomized, single-dose, 4-period/treatment, crossover study that assessed the relative BA of estrogens and MPA from 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, 2 x 0.3 mg CE/1.5 mg MPA, and 2 x 0.3 mg CE alone oral tablets.
4. Sponsor conducted a clinical safety and efficacy study (0713D2-309-US; HOPE study) to support NDA 20-527 SLR-017.
5. Bioanalytical reports together with validation reports for the determination of unconjugated and total estrone (baseline adjusted and unadjusted), equilin, 17β-estradiol (baseline adjusted and unadjusted), 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol in plasma via [redacted] and MPA in plasma via radioimmunoassay for the 2 clinical pharmacokinetics (PK) studies were provided (volumes 34 and 35 of 88).
6. Study reports for the 2 clinical PK studies were provided.
7. Separate in vitro dissolution methods and data for CE and MPA from various CE/MPA tablet formulations used in the clinical safety and efficacy as well as PK studies were provided (Table

6.1.6A volume 19 of 88); however, those data were based on the USP 22 and 23 methods (disintegration apparatus, simulated gastric fluid media, and 15 minutes time points for 1 hour of content released) for conjugated estrogens containing tablets. The proposed in vitro dissolution methods and specifications for CE from the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA oral tablets were based on the USP 24 method (USP Apparatus 2, water as medium, and at 2, 5, and 8 hours time points of content released). The difference in in vitro dissolution methods is a review issue. The proposed in vitro dissolution methods and specifications for MPA from the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA oral tablets were provided.

8. The formulations (CE/MPA and CE) tested in the clinical studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the market formulations in terms of scale of manufacture and composition except the color coat, which was white in the clinical formulation (Section 6.1.4 volume 19 of 88). Comparisons of in vitro dissolution data based on the USP 24 method for the formulation tested in the clinical safety and efficacy study versus that of the to-be-marketed formulation were not provided.
9. Labeling for the Clinical Pharmacology section was provided. However, no references or annotation were provided for the labeling.
10. PK data for studies 0713D2-119-US and 0713D2-120-US in electronic diskettes (ASCII format) with user guide will aid the review as well as study reports and Human Pharmacokinetics and Biopharmaceutics summary in Word 97 software files will aid the NDA review.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) found that the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017 is fileable. Comments 8 to 10 above should be communicated to and addressed by the sponsor.

/S/ October 3, 2000

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 10/ 3 /00

cc: NDA 20-527, HFD-870 (H. Malinowski, J. Hunt, A. Parekh, J. Lau), HFD-580 (T. van der Vlugt, D. Lin, D. Moore), CDR (B. Murphy for Drugs)

TABLE 6.1.2.2A. TABLE OF COMPARATIVE BIOAVAILABILITY STUDIES WITH VARIOUS ORAL DOSES OF CE AND MPA

Protocol No. Report No. (Investigator)	Study Design	Dose	Batch No.	No. in PK Analysis (sex)[a] [ethnic][b] {age}[c]	Applicant Conclusion
0713D2-119-US GMR-32506 (KC Lasseter) Vol. 20 / 1 Vol. 37 / 1	Randomized, single-dose, 4-period, 4-treatment, crossover phase I study of the comparative bioavailability of estrogens and MPA from 3 strengths of CE/MPA combination tablets and 1 strength of a tablet of CE alone	CE/MPA Group A. 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/2.5 mg Group C: 2 x 0.45 mg/1.5 mg CE alone Group D: 2 x 0.45 mg	A. 2TQA B: 3TEN C: 3TEM D: 3TEL	31 (31F) [1W, 34 H] {39 - 65, 57}	Two tablets of CE/MPA 0.45 mg/2.5 mg or 0.45 mg/1.5 mg, or 2 CE 0.45 mg tablets produced lower estrogen concentrations than did 2 combination tablets of 0.625 mg/2.5 mg. MPA concentrations were lower with CE/MPA 0.45 mg/1.5 mg than with 0.625 mg/2.5 mg or 0.45 mg/2.5 mg. Estrogens and MPA behaved pharmacokinetically in a dose-related manner.
0713D2-120-US GMR-32507 (R Salzer) Vol. 27 / 1 Vol. 44 / 1	Randomized, single-dose, 4-period, 4-treatment, crossover, phase I study of the comparative bioavailability of estrogens and MPA from 3 strengths of CE/MPA combination tablets and 1 strength of a tablet of CE alone	CE/MPA Group A. 2 x 0.625 mg/2.5 mg Group B: 2 x 0.45 mg/1.5 mg Group C: 2 x 0.30 mg/1.5 mg CE alone Group D: 2 x 0.30 mg	A. 2TQA B. 3 TEM C. 3 THN D. 3THP	30 (30F) [29W, 5B] {38-65, 54}	Two tablets of CE/MPA 0.30 mg/1.5 mg or CE 0.30 mg produced lower estrogen concentrations than did 2 combination tablets of 0.625 mg/2.5 mg or 0.45 mg/1.5 mg tablets. MPA concentrations were lower with CE/MPA 0.30 mg/1.5 mg or 0.45 mg/1.5 mg than with 0.625 mg/2.5 mg tablets. MPA had no effect on the pharmacokinetics of CE estrogen components.

a: Sex: F = female.
b: Ethnic origin: W = white, B = black, H = Hispanic
c: Age: min - max, mean in years

NDA 20-527/S-017
Conjugated estrogens and medroxyprogesterone acetate tablets, 0.3 mg/1.5 mg and 0.45 mg/1.5 mg
Wyeth-Ayerst Laboratories, Inc.

End of Phase 2 and Pre-NDA meetings

No End of Phase 2 or Pre-NDA meetings were held for this efficacy supplement.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-527 SLR-017**
Compound:	0.45 or 0.3 mg conjugated estrogens and 1.5 mg medroxyprogesterone acetate
Sponsor:	Wyeth-Ayerst Research
Type of Submission:	Efficacy Supplement
Submission Dates:	20-527 SLR-017, June 15, 2000; SE2-017-BB: October 24, 2000 and February 28, 2001; SE2-017-BC: April 11, 2001 and April 12, 2001; SE2-017-BL: April 11, 2001; SE2-017-C: April 12, 2001.
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Synopsis:

NDA 20-527 SLR-017 ([redacted] , proposes 2 oral tablets, 0.45 mg conjugated estrogens (CE)/1.5 mg medroxyprogesterone acetate (MPA) or 0.3 mg CE/1.5 mg MPA, in a continuous combined regimen for the treatment of moderate to severe vasomotor symptoms associated with menopause, and [redacted] vulvar and vaginal atrophy was submitted on June 15, 2000.

Sponsor conducted a clinical safety and efficacy study (0713D2-309-US; Health and Osteoporosis. Progestin and Estrogen (HOPE) study for CE and MPA) to support NDA 20-527 SLR-017. Sponsor conducted 2 relative bioavailability studies (0713D2-119-US and 0713D2-120-US) to support the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017. These 2 studies are identical in design (randomized, single-dose, 4-period/treatment, crossover) except different CE and MPA combination strengths were administered. Study 0713D2-119-US concerns 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, and 2 x 0.45 mg CE alone oral tablets. Whereas, Study 0713D2-120-US concerns 2 x 0.625 mg CE/2.5 mg MPA, 2 x 0.45 mg CE/1.5 mg MPA, 2 x 0.3 mg CE/1.5 mg MPA, and 2 x 0.3 mg CE alone oral tablets. The formulations (CE/MPA and CE) tested in the clinical Studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the market formulations in terms of scale of manufacture and composition except the color coat, which was white in the clinical formulations. This color change between the clinical batch and to-be-marketed batch was justified via in vitro dissolution data.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB DPEII) has reviewed NDA 20-527 SLR-017 dated June 15, 2000. OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section of NDA 20-527 SLR-017.

- Sponsor's proposed conjugated estrogens in vitro dissolution method (USP XXIV apparatus 2, 900 mL water, 37°C, and 50 rpm) is acceptable. However, the recommended conjugated estrogens in vitro dissolution specifications for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% estrone sulfate released
2 hours	[redacted]
5 hours	[redacted]
8 hours	[redacted]

Sponsor accepted the recommended conjugated estrogens in vitro dissolution specifications per sponsor's April 12, 2001 letter.

- Sponsor's proposed medroxyprogesterone acetate in vitro dissolution method via USP disintegration apparatus (0.54% sodium lauryl sulfate, 900 mL, 37°C, and 30 dips/min) is acceptable on an interim basis. The recommended medroxyprogesterone acetate specification for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate oral tablets are:

Time	% medroxyprogesterone acetate released
30 minutes	Not less than [redacted]

Sponsor accepted the recommended medroxyprogesterone acetate in vitro dissolution specifications per sponsor's April 11, 2001 letter.

- Sponsor should develop the medroxyprogesterone acetate dissolution methods via the USP in vitro dissolution apparatuses (such as basket and paddle) for the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets as well as the other approved strengths of conjugated estrogens and medroxyprogesterone acetate tablets as a Phase IV commitment. The final dissolution specifications for the medroxyprogesterone acetate components of the 0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate tablets will be based on data via the USP in vitro dissolution apparatus. Per sponsor's April 12, 2001 letter, sponsor is committed to in vitro dissolution feasibility study via the [redacted]™ and provide the FDA with the new in vitro dissolution method and preliminary data for comments approximately 4 months after approval.
- Sponsor's Clinical Pharmacology labeling changes per teleconference on April 12, 2001 are accepatble.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 20-527 SLR-017 was conducted on March 19, 2001; participants included D. Moore, D. Lin, H. Malinowski, J. Hunt, A. Parekh, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader 4/ /01

cc: NDA 20-527, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (T. van der Vlugt, D. Moore), HFD-820 (D. Lin), CDR (B. Murphy for Drugs)

Background:
Sponsor also submitted NDA 04-782 SE2-115 for the 0.45 mg CE alone oral tablet on July 31, 2000 for the same indications. PREMARIN® is available as 0.3, 0.625, 0.9, 1.25, and 2.5 mg CE alone oral tablets. PREMPRO™ is available as 0.625 mg CE/2.5 mg MPA or 0.625mg CE/5 mg MPA oral tablets for continuous combined administration. PREMARIN® is derived from pregnant mares' urine, which contains more than 10 estrogens, including the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone. MPA is a synthetic progestin derived from 17α-hydroxyprogesterone. Other background material has been covered in the synopsis section above. General CE and MPA clinical pharmacokinetic information is in the PREMPRO™ labeling. Synopses for Studies 0713D2-119-US and 0713D2-120-US are in Attachment 1.

The following questions, based on the content of NDA 20-527 SLR-017, guided this review.

1. What studies results are submitted to support the Human Pharmacokinetics (PK) and Bioavailability (BA) section of NDA 20-527 SLR-017?

	Study	Review Question
Bioanalytical assay	-	2
Relative BA	0713D2-119-US and 0713D2-120-US	3
Dose proportionality	0713D2-119-US and 0713D2-120-US	4
Multiple dose	-	5
Interaction between CE and MPA	0713D2-120-US and NDA 20-303*	6
Formulation	-	7
In vitro dissolution	-	8
Proposed labeling	-	9

*Sponsor referenced Study 713B-103-US in NDA 20-303.

2. What are the bioanalytical methods for CE and MPA used in NDA 20-527 SLR-017?
For both Studies 0713D2-119-US and 0713D2-120-US, sponsor used the same bioanalytical methods. Because of low doses, 2 tablets of each formulation were administered to provide plasma drug concentrations that could be more accurately measured.

Unconjugated and total estrone (baseline adjusted and unadjusted), equilin, 17β-estradiol (baseline adjusted and unadjusted), 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol in plasma were determined via [redacted] Total (unconjugated and conjugated) estrone, equilin, $\Delta^{8,9}$-dehydroestrone, 17β-estradiol, 17β-dihydroequilin and 17β-$\Delta^{8,9}$-dehydro-estradiol concentrations in plasma were determined via the same procedure after [redacted] Control samples were also utilized to confirm that the hydrolysis of the conjugated estrogens was complete. The %CV for CE analytes ranged from 5.1 to 14.0 for both Studies 0713D2-119-US and 0713D2-120-US.

MPA in plasma was determined via radioimmunoassay. The inter-assay coefficients of variation of the quality control samples for the MPA analytical runs ranged from 7.8% to 10.9% for Study 0713D2-119-US and from 6.3% to 7.8% for Study 0713D2-120-US.

Analyte	¶LLOQ, pg/mL
2 mL plasma sample:	
unconjugated estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	
Unconjugated equilin	
Unconjugated 17β-estradiol	
0.4 mL plasma sample:	
Total equilin	
total estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	
Total 17β-estradiol	
medroxyprogesterone	

¶LLOQ = lower limit of quantitation

See Attachment 2 for bioanalytical assay validations for Studies 0713D2-119-US and 0713D2-120-US.

Overall, the bioanalytical assays for CE and MPA in plasma were acceptable. However, the CE inter-day coefficient table for Study 0713D2-119-US were not consistent between the study report and the bioanalytical report (slight variations in reported numbers; Attachment 2). Whereas, the CE inter-day coefficient table for Study 0713D2-120-US were consistent between the study report and bioanalytical report. Sponsor did not summarize and report the intra-day variation for CE and MPA bioanalytical assays.

3. What is the relative BA of the CE/MPA oral tablets?

See Attachment 3 for CE and MPA figure and PK parameters tables, which were combined for Studies 0713D2-119-US and 0713D2-120-US.

Study 0713D2-119-US

The comparative BA for CE components and MPA were evaluated following single dose oral administration of 2 x 0.625 mg CE/2.5 mg MPA tablets (treatment A), 2 x 0.45 mg CE/2.5 mg MPA tablets (treatment B), 2 x 0.45 mg CE/1.5 mg MPA tablets (treatment C), and 2 x 0.45 mg CE tablets (treatment D). All of the CE with estimable peak concentration (C_{max}) and area under the concentration-time curve (AUC) showed significant treatment differences for these parameters. In general, results of the Duncan's Multiple Range Test indicated that the three 0.45 mg CE treatments produced lower CE concentrations than that for the 0.625 mg CE treatment. The ratios of mean C_{max} for estrogens observed following treatments B, C, and D to mean C_{max} following treatment A ranged from 56% to 76%; and the ratios of mean AUC ranged from 57% to 84%. The theoretical value for CE C_{max} ratio and AUC ratio (0.45/0.625) were 72%.

Significant treatment differences were seen for C_{max} and AUC of MPA, and the Duncan's Multiple Range Test indicated that the 1.5 mg MPA treatment produced lower MPA concentrations than the two 2.5 mg MPA treatments. The ratios of mean C_{max} following treatment C to mean C_{max} following treatments A and B were 53% and 68%, respectively; and the ratios of mean AUC were 62% and 63%, respectively (the theoretical value for MPA C_{max} ratio and AUC ratio (1.5/2.5) were 60%).

Study 0713D2-120-US

The comparative BA for CE and MPA were evaluated following single dose oral administration of 2 x 0.625 mg CE/2.5 mg MPA tablets (treatment A), 2 x 0.45 mg CE/1.5 mg MPA tablets (treatment B), 2 x 0.3 mg CE/1.5 mg MPA tablets (treatment C), and 2 x 0.3 mg CE tablets (treatment D). All of the

CE with estimable C_{max} and AUC showed significant treatment differences for these parameters. In general, results of the Duncan's Multiple Range Test indicated that the lower-dose treatments with CE (treatments B, C, and D) produced lower rank-order estrogen concentrations than that for the 0.625 mg CE treatment (A). The theoretical ratio of the estrogen concentrations for the 0.45 mg CE dose to that for the 0.625 mg CE dose is 72%. The CE ratios of mean C_{max} for treatment B (0.45 mg) to mean C_{max} for treatment A (0.625 mg) ranged from 56% to 63%, and the ratios of mean AUC ranged from 64% to 75%. The theoretical ratio of the estrogen concentrations for the 0.3 mg CE dose to that for the 0.625 mg CE dose is 48%. The CE ratios of mean C_{max} for treatments C and D (0.3 mg) to those of mean C_{max} for treatment A (0.625 mg) ranged from 46% to 54%, and the ratios of mean AUC ranged from 45% to 59%.

Significant treatment differences were seen for C_{max} and AUC of MPA; the Duncan's Multiple Range Test indicated that the two 1.5 mg MPA treatments produced lower MPA concentrations than that for the 2.5 mg MPA treatment. The ratios of mean C_{max} following treatments B and C to the mean C_{max} for treatment A were 70% and 77%, respectively; and the ratios of mean AUC were 72% and 70%, respectively (the theoretical value for MPA C_{max} ratio and AUC ratio (1.5/2.5) were 60%).

4. Are CE or MPA dose proportional kinetically?

Sponsor used a power model ($y_{ij} = \alpha \bullet (D_j)^{\beta}$; Attachment 4) to fit the dose-dependent PK parameter (y_{ij} represents C_{max}, AUC_t, or AUC after the jth dose for the ith subject and D_j is the amount of the jth dose; α depends on the subject and error; and β is an indicator of dose proportionality. A log transformation of the data was used to linearize the equation ($\log (y_{ij}) = \log (\alpha) + \beta \bullet \log (D_j)$). Exact dose proportionality requires that $\beta = 1$ for dose-dependent parameters; for empirical estimates of β, the value of 1 should be within the 95% confidence limit for β.

Most of the components showed linear dose proportionality (Attachment 4), except unconjugated equilin AUC_t, unconjugated 17β-estradiol C_{max}, unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol C_{max} and AUC_t, and total $\Delta^{8,9}$-dehydroestrone C_{max} and AUC. Sponsor attributed these observations to: **1.** different formulations administered in the 2 studies, **2.** 2 studies were combined for analysis but did not incorporate a complete, randomized crossover design, and **3.** the small (2-fold) range of doses and the statistical power was not large enough for typical dose-proportionality studies. Per discussion with pharmacometric reviewer, Dr. He Sun, sponsor's rationale above is acceptable because: *1.* The 0.45 mg CE group is associated with different amount of MPA (2.5, 1.5, and 0 mg) administered. The 0.3 mg CE group is associated with different amount of MPA (1.5 and 0 mg) administered. Therefore, formulation differences. *2.* These are cross study comparisons. When Studies 0713D2-119-US and 0713D2-120-US are pooled together, there are 2 groups of 0.625 mg CE/2.5 mg MPA treatment, 2 groups of 0.45 mg CE/1.5 mg MPA treatment, and 1 group of 0.45 mg CE/2.5 mg MPA, 0.3 mg CE/1.5 mg MPA, 0.45 mg CE alone, and 0.3 mg CE alone treatment each. Therefore, across studies difference. *3.* Unequal weight contributed from different treatment groups with the 2-fold range of dose (different number of treatment groups as in rationale *2* above).

See tables in Attachment 3 for MPA PK and dose proportionality data. MPA was absorbed more rapidly than CE; mean CE t_{max} was about 2 - 4 hours. MPA $t_{1/2}$ was about 40 - 50 hours. MPA C_{max} and AUC increased in a linear dose-proportional manner.

5. Do CE or MPA accumulate upon multiple dose administration of 0.45 mg CE/1.5 mg MPA or 0.3 mg CE/1.5 mg MPA oral tablets?

Both Studies 0713D2-119-US and 0713D2-120-US are single dose in design and did not address the dose accumulation potential upon multiple-dose administration. PREMPRO™ 0.625 mg CE/2.5 mg MPA and 0.625mg CE/5 mg MPA oral tablets for continuous combined administration were approved for the same indications as that for 0.45 mg CE/1.5 mg MPA or 0.3 mg CE/1.5 mg MPA oral tablets via this efficacy supplement. No multiple dose PK information is in the current PREMPRO™ labeling. Sponsor has Study 0713D2-309-US in NDA 20-527 SLR-017 to demonstrate the safety and efficacy of 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA oral tablets; no blood was sampled for CE and MPA measurements in this study. However, the Division of Biopharmaceutics recommended that blood drug concentrations of CE and MPA should be determined in the required Phase IV clinical study (see Attachment 5). Lack of multiple dose PK information for 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA tablets may not be a critical issue for this efficacy supplement.

6. What is the drug interaction potential between CE and MPA upon oral administration of CE/MPA?

Study 0713D2-120-US showed that oral, single-dose, concomitant administration of 0.6 mg CE/3 mg MPA (2 x 0.3 mg CE/1.5 mg MPA) did not alter the PK of CE as compared to that for the 0.6 mg CE alone (2 x 0.3 mg CE). Virtually all CE parameters were within the 80 - 125% of the 90% confidence interval for C_{max} and AUC (Attachment 6). These data were consistent with those data observed in Study 713B-103-US for NDA 20-303 (sponsor referenced this study), which single dose 1.25 mg CE and 10 mg MPA (2 x 0.625 mg CE alone Premarin tablets, 2x 5 mg MPA alone tablets, and 2 x 0.625 mg CE Premarin tablets plus 2 x 5 mg MPA tablets) were administered. No PK interaction was observed in Study 713B-103-US; see Attachment 6 for the Clinical Pharmacology and Biopharmaceutics review for Study 713B-103-US. Therefore, these data showed that coadministration with MPA does not alter CE PK upon single dose administration. Moreover, current PREMPRO™ and PREMPHASE® labeling has these statements in the labeling "Coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA. Similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens."

Study 0713D2-119-US has the CE alone treatment group (2 x 0.45 mg). Sponsor could have used the same approach that was used in Study 0713D2-120-US above to analyze the drug interaction potential between 2 x 0.45 mg CE/1.5 mg MPA and 2 x 0.45 mg CE. However, sponsor's bracketing approach (1.25 mg CE/10 mg MPA to 0.6 mg CE/3 mg MPA) to address between CE and MPA oral administration is acceptable.

7. What are the formulations used in the clinical studies for NDA 20-527 SLR-017?

The CE/MPA formulations consist of a core tablet containing CE, which is coated with [redacted]. The formulations (CE/MPA and CE) tested in the clinical Studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the market formulations in terms of scale of manufacture and composition except the [redacted] for the clinical formulation. See Attachment 7 for formulation information.

Sponsor submitted the in vitro dissolution data to substantiate the similarity between the clinical batch and to-be-marketed batch on February 28, 2001 (see Attachment 7). For the 0.3 mg CE/1.5 mg MPA

and 0.45 mg CE/1.5 mg MPA tablet, each strength has 2 clinical batches and 3 market batches. For each combination strength, namely 0.3 mg CE/1.5 mg MPA or 0.45 mg CE/1.5 mg MPA tablet, this reviewer chose 1 clinical batch and 1 market batch that had the largest %CV of CE released and plotted the % CE released versus time (see Attachment 8). The f_2 calculations cannot be applied since the data were collected at different time points between the clinical and market batch. By overlaying the dissolution profiles between the clinical batch over the market batch, the CE dissolution profiles appear to be similar for the 0.3 mg CE/1.5 mg MPA or 0.45 mg CE/1.5 mg MPA tablets despite the color change. The MPA in vitro dissolution data also showed similarity via inspection between the clinical batches and market batches for the 0.3 mg CE/1.5 mg MPA or 0.45 mg CE/1.5 mg MPA tablets (see Attachment 7).

8. What are the proposed in vitro dissolution method and specifications for 0.3 mg CE/1.5 mg MPA or 0.45 mg CE/1.5 mg MPA tablets?

Sponsor's in vitro dissolution method for CE:	
Apparatus	USP XXIV apparatus 2 (paddle)
In vitro release medium	water
Volume of release medium	900 mL
Medium temperature	37 °C
Stirring speed	50 rpm

CE in vitro dissolution specifications:

	Recommended, % estrone sulfate released	Proposed, % estrone sulfate released
2 hours	Not more than —	—
5 hours	—	—
8 hours	Not less than —	

Sponsor's in vitro dissolution method for MPA:	
Apparatus	USP disintegration Apparatus
In vitro release medium	0.54% sodium lauryl sulfate
Volume of release medium	900 mL
Temperature	37 °C
Dip rate	30 dips/min

MPA in vitro dissolution specifications:

	Recommended, % MPA released	Proposed, % MPA released
15 minutes		
30 minutes	Not less than —	
45 minutes		—
60 minutes		

Sponsor proposed USP XXIV apparatus 2 (paddle) method to be the dissolution method for CE and the proposed sampling time points were 2, 5, and 8 hours. The sampling time for the clinical batch that used the proposed method (1, 2, 4, 6, and 10 hours) was different from that for the to-be-marketed batch (2, 5, and 8 hours), which made it difficult to use the clinical batch to set specifications. Since the clinical batch differs from the to-be-marketed batch by color only and the in vitro dissolution data justified that the clinical and to-be-marketed batches are similar (Question 7 above), the to-be-

marketed batches were used to set the CE in vitro dissolution specifications for 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA tablets instead. See Attachment 9 for CE in vitro dissolution data for the marketed batch. The recommended CE dissolution specifications at 2 and 5 hours are "not more than [redacted] " estrone sulfate released, respectively. In vitro estrone sulfate dissolution represents the dissolution behavior of all the conjugated estrogens components. The rationale for this recommendation is to be consistent with the conjugated estrogens tablets' in vitro dissolution specifications in USP 24 ("19 - 49%" and "66 - 96%" estrone sulfate released at 2 and 5 hours, respectively). The recommended 8 hours data point slightly tightens the proposed dissolution specifications for CE.

The proposed MPA in vitro dissolution method and specifications were based on the approved MPA in vitro dissolution method and specifications (Method 2555-131 for 0.625 mg CE/2.5 mg MPA and 0.625 mg CE/5 mg MPA tablets), which were approved on an interim basis (see Attachment 9). Sponsor had a Phase IV commitment to develop an MPA in vitro dissolution method for NDA 20-527 (0.625 mg CE/2.5 mg MPA and 0.625 mg CE/5 mg MPA tablets). Sponsor submitted preliminary results for the development of MPA in vitro dissolution test for 0.625 mg CE/2.5 mg MPA and 0.625 mg CE/5 mg MPA tablets on March 20, 1997. It was sent for Dr. Vinod Shah's consult, which is pending (Attachment 9). During the Optional Intradivision Clinical Pharmacology and Biopharmaceutics briefing on March 19, 2001, it is recommended that sponsor should develop MPA in vitro dissolution methods via the USP in vitro dissolution apparatuses (such as basket and paddle) for the 0.45 mg CE/1.5 mg MPA and 0.3 mg CE/1.5 mg MPA tablets. The MPA in vitro dissolution data for the clinical and market batches support the recommended "not less than [redacted] ' MPA released at 30 minutes (Attachment 7).

9. What are sponsor's proposed labeling for products' Clinical pharmacology section?
In the future, the Clinical Pharmacology section for PREMARIN®, PREMPRO™, and PREMPHASE® labeling should be consistent to each other. Due to the length of sponsor's proposed labeling, only the clinical pharmacology section will be presented in Attachment 10. Labeling comments follow (unwanted parts are deleted and added parts are double underscored):

CLINICAL PHARMACOLOGY

[redacted]

Number of Pages Redacted 3

Draft Labeling
(not releasable,

Attachment 1

STUDY TITLE: A SINGLE-DOSE, COMPARATIVE BIOAVAILABILITY STUDY OF PREMARIN AND MEDROXYPROGESTERONE-ACETATE (MPA) FROM THREE STRENGTHS OF PREMARIN/MPA COMBINATION TABLETS AND ONE STRENGTH OF A PREMARIN-ONLY TABLET IN HEALTHY, POSTMENOPAUSAL WOMEN: FINAL REPORT (Protocol **0713D2-119-US**, GMR-32506)

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

PUBLICATION (REFERENCE): N/A

STUDY PERIOD : **CLINICAL PHASE:** I

(DATE OF FIRST ENROLLMENT) 28 Aug 1996
(DATE OF LAST COMPLETION) 20 Jan 1997

OBJECTIVES: To assess the relative bioavailability of Premarin and MPA contained in three different strengths of Premarin/MPA combination tablets and that of a Premarin-only tablet in healthy, hysterectomized, postmenopausal women.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy women 35 to 65 years old who were within ± 20% of ideal body weight for their height and frame. The subjects had to be hysterectomized ambulatory women who were either naturally postmenopausal, with little or no ovarian estrogen production, or who had a bilateral oophorectomy (documented by an operative report) because of benign pathologic findings at least 6 months before the study start.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):
32 planned, 35 enrolled, 32 completed, 31 analyzed.

DURATION OF TREATMENT: Each subject participated in the clinical portion of the study for approximately 99 days, which included four 9-day study periods with at least 30-day washout intervals. Each study period consisted of a 2 ½-day (3 night) inpatient stay and 6 outpatient visits. The duration of the study was 5 months.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Treatment A: two tablets of Premarin 0.625 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 2TQA. Treatment B: two tablets of Premarin 0.45 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 3TEN. Treatment C: two tablets of Premarin 0.45 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3TEM. Treatment D: two tablets of Premarin 0.45 mg, batch no. 3TEL.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

PHARMACOKINETIC AND STATISTICAL METHODS: Noncompartmental pharmacokinetic methods were used to analyze the plasma concentration data. Statistical comparisons were made by using an analysis of variance (ANOVA) for a four-period crossover design. Pairwise comparisons between treatments were made by using Duncan's Multiple Range Test for p-values ≤ 0.05.

SAFETY ASSESSMENT METHODS: A complete medical, gynecologic, and physical examination, with measurement of vital signs and hematologic, biochemical, renal, hepatic, and urinary laboratory determinations, was done at screening and study completion. During the treatment period, study events and symptoms, as well as vital signs and concomitant medications, were evaluated and recorded in the case report form.

PHARMACOKINETIC RESULTS: The comparative bioavailabilities for Premarin components and MPA were evaluated following administration of two Premarin 0.625-mg/MPA 2.5-mg tablets (treatment A), two Premarin 0.45-mg/MPA 2.5-mg tablets (treatment B), two Premarin 0.45-mg/MPA 1.5-mg tablets (treatment C), and two Premarin 0.45-mg tablets (treatment D). All of the Premarin estrogens with estimable peak concentration (C_{max})and area under the concentration-time curve (AUC) showed significant treatment differences for these parameters. In general, results of the

Duncan's Multiple Range Test indicated that the three 0.45-mg Premarin treatments produced lower estrogen concentrations than the 0.625-mg Premarin treatment. The ratios of mean C_{max} for estrogens observed following treatments B, C, and D to mean C_{max} following treatment A ranged from 56% to 76%; and the ratios of mean AUC ranged from 57% to 84%, which are reasonably close to the theoretical value of 72%.

Significant treatment differences were seen for C_{max} and AUC of MPA, and the Duncan's Multiple Range Test indicated that the 1.5-mg MPA treatment produced lower MPA concentrations than the two 2.5-mg MPA treatments. The ratios of mean C_{max} following treatment C to mean C_{max} following treatments A and B were 53% and 68%, respectively; and the ratios of mean AUC were 62% and 63%, respectively, which are very close to the theoretical value of 60%.

SAFETY RESULTS: There were no serious or unexpected adverse events. All events were treatment emergent; headache was the most common adverse event. Eight (8) headaches were reported by 7 subjects; all but 1 of these were considered to be possibly drug related. One (1) headache (drug-related) was severe. There were isolated increases and decreases from baseline in laboratory values, vital signs, and weight, but none of these were considered clinically important.

CONCLUSION: The two —— , two Premarin 0.45-mg/MPA 1.5-mg combination tablets, and two Premarin 0.45-mg tablets produced lower estrogen concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, in line with the relative doses. The two Premarin 0.45-mg/MPA 1.5-mg combination tablets produced lower MPA concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, or the two —— —approximately 60% of the larger MPA dose. The various dose strengths of Premarin and MPA behave pharmacokinetically in a dose-proportional manner.

DATE OF THE REPORT: 09 Jul 1999

STUDY TITLE: A SINGLE-DOSE, COMPARATIVE BIOAVAILABILITY STUDY OF PREMARIN AND MEDROXYPROGESTERONE ACETATE (MPA) FROM THREE STRENGTHS OF PREMARIN/MPA COMBINATION TABLETS AND ONE STRENGTH OF A PREMARIN-ONLY TABLET IN HEALTHY, POSTMENOPAUSAL WOMEN: FINAL REPORT (Protocol **0713D2-120-US**, GMR-32507)

INVESTIGATORS: [redacted]).

STUDY CENTERS: [redacted]

PUBLICATION (REFERENCE): N/A

STUDY PERIOD : **CLINICAL PHASE:** I
(DATE OF FIRST ENROLLMENT) 14 Sep 1996
(DATE OF LAST COMPLETION) 14 Feb 1997

OBJECTIVES: To assess the relative bioavailability of Premarin and MPA contained in three different strengths of Premarin/MPA combination tablets and that of a Premarin-only tablet in healthy, hysterectomized, postmenopausal women.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy women 35 to 65 years old who were within ± 20% of ideal body weight for their height and frame. The subjects had to be hysterectomized ambulatory women who were either naturally postmenopausal, with little or no ovarian estrogen production, or who had a bilateral oophorectomy (documented by an operative report) because of benign pathologic findings at least 6 months before the study start.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):
32 planned, 34 enrolled, 30 completed, 30 analyzed.

DURATION OF TREATMENT: Each subject participated in the clinical portion of the study for approximately 99 days, which included four 9-day study periods with at least 30-day washout intervals. Each study period consisted of a 2 ½-day (3 night) inpatient stay and 6 outpatient visits. The duration of the study was 5 months.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Treatment A: two tablets of Premarin 0.625 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 2TQA. Treatment B: two tablets of Premarin 0.45 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3 TEM. Treatment C: two tablets of Premarin 0.30 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3 THN. Treatment D: two tablets of Premarin 0.30 mg, batch no. 3THP.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

PHARMACOKINETIC AND STATISTICAL METHODS: Noncompartmental pharmacokinetic methods were used to analyze the plasma concentration data. Statistical comparisons were made by using an analysis of variance (ANOVA) for a four-period crossover design. Pairwise comparisons between treatments were made by using Duncan's Multiple Range Test for p-values ≤ 0.05.

SAFETY ASSESSMENT METHODS: A complete medical, gynecologic, and physical examination, with measurement of vital signs and hematologic, biochemical, renal, hepatic, and urinary laboratory determinations, was done at screening and study completion. During the treatment period, study events and symptoms, as well as vital signs and concomitant medications, were evaluated and recorded in the case report form.

PHARMACOKINETIC RESULTS: The comparative bioavailabilities for Premarin estrogen components and MPA were evaluated following administration of two Premarin 0.625-mg/MPA 2.5-mg tablets (treatment A), two Premarin 0.45-mg/MPA 1.5-mg tablets (treatment B), two Premarin 0.30-mg/MPA 1.5-mg tablets (treatment C), and two Premarin 0.30-mg tablets (treatment D). All of the Premarin estrogens with estimable peak concentrations (C_{max}) and areas under the concentration-time curve (AUC) showed significant treatment differences for these parameters, as expected. In general, results of the Duncan's Multiple Range Test indicated that the lower-dose treatments with Premarin (B, C, and D) produced lower rank-order estrogen concentrations than the Premarin 0.625-mg treatment (A). The ratio of the estrogen

concentrations for the Premarin 0.45-mg dose and the 0.625-mg dose, respectively, is 72%. The Premarin estrogen ratios of mean C_{max} for treatment B (0.45 mg) to those of mean C_{max} for treatment A (0.625 mg) ranged from 56% to 63%, and the ratios of mean AUC ranged from 64% to 75%. The ratio of the estrogen concentrations for the Premarin 0.30-mg dose and the 0.625-mg dose, respectively, is 48%. The Premarin estrogen ratios of mean C_{max} for treatments C and D (0.30 mg) to those of mean C_{max} for treatment A (0.625 mg) ranged from 46% to 54%, and the ratios of mean AUC ranged from 45% to 59%. These ratios are similar to the theoretical values, especially for the more reliable AUC values, and thus demonstrate that the estrogen components are dose proportional in this dose range.

Significant treatment differences were seen for C_{max} and AUC of MPA, as expected; the Duncan's Multiple Range Test indicated that the two 1.5-mg MPA treatments produced lower MPA concentrations than the 2.5-mg MPA treatment. The ratios of mean C_{max} following treatments B and C to the mean C_{max} for treatment A were 70% and 77%, respectively; and the ratios of mean AUC were 72% and 70%, respectively, which are reasonably close to the theoretical value of 60%.

Comparison of estrogen pharmacokinetic parameters following administration of 2 x Premarin 0.30- mg/MPA 1.5-mg combination tablets and 2 x Premarin 0.30-mg tablets demonstrates that there is no effect of MPA on Premarin estrogen pharmacokinetics.

SAFETY RESULTS: There were no serious or unexpected adverse events. Twenty-one (21) events were reported during the study; all were treatment emergent. Four (4) subjects reported prestudy events of mild or moderate severity. Headache was the most common drug-related adverse event (7/34, 21%), as well as the most common adverse event regardless of drug relationship (12/34, 35%). All headaches were mild to moderate. An accidental injury not related to the study medication was the only severe event. There were isolated increases and decreases from baseline in laboratory values and vital signs, but none of these were considered clinically important.

CONCLUSION: The two Premarin 0.30-mg/MPA 1.5-mg combination tablets and two Premarin 0.30-mg tablets produced lower estrogen concentrations than the two Premarin 0.45-mg/MPA 1.5-mg combination tablets and the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, in line with the relative doses. Likewise, the two Premarin 0.45-mg/MPA 1.5-mg combination tablets produced lower estrogen concentrations than the two Premarin 0.625-mg MPA 2.5-mg combination tablets. Furthermore, the two Premarin 0.30-mg/MPA 1.5-mg combination tablets and the two Premarin 0.45-mg/MPA 1.5-mg combination tablets produced lower MPA concentrations than the two 0.625-mg/MPA 2.5-mg combination tablets. The various dose strengths of Premarin and MPA in these combination tablets result in plasma concentrations that appear to increase in a dose-proportional manner. However, because different formulations were used and thus confounded the statistical comparison, linear dose-proportionality cannot be concluded in this study. Based on a drug interaction analysis, MPA has no effect on the pharmacokinetics of Premarin estrogen components.

DATE OF THE REPORT: 16 Dec 1999

Attachment 2

The CE inter-day coefficient of variation (%CV) and the mean bias for the low, mid, and high quality control samples are summarized below for Study 0713D2-119-US (from *study report*).

TABLE 6.5.2A. INTER-DAY COEFFICIENT OF VARIATION (% CV) AND MEAN BIAS

		-----Unconjugated-----		----------Total---------	
Analyte	QC	% CV	% Bias	% CV	% Bias
Estrone	Low	9.7	6.7	13.3	0.0
	Mid	5.7	-3.1	3.1	-1.1
	High	6.0	-1.4	4.0	0.4
Equilin	Low	6.5	1.3	7.6	-1.0
	Mid	3.4	-3.0	4.1	-2.0
	High	4.8	-1.3	5.5	-1.6
$\Delta^{8,9}$-Dehydroestrone	Low	14.3	-8.0	7.6	-8.7
	Mid	7.6	-3.5	19.1	-6.7
	High	5.2	-5.0	6.4	1.0
17β-Estradiol	Low	11.6	2.9	14.9	-2.7
	Mid	6.6	1.2	3.9	3.4
	High	4.8	1.0	3.9	3.5
17β-Dihydroequilin	Low	8.6	-2.7	4.3	4.0
	Mid	6.1	-3.9	4.2	-3.2
	High	7.9	-2.5	5.5	-1.5
17β-$\Delta^{8,9}$-Dehydroestradiol	Low	11.5	-5.3	7.7	-4.7
	Mid	4.9	-4.9	15.0	-5.5
	High	4.0	-4.0	7.7	-2.0

Study 0713D2-119-US:

Analyte	Standard curve range, pg/mL
Estrone	5 - 1000
Equilin	10 - 1000
$\Delta^{8,9}$-Dehydroestrone	5 - 250
17β-Estradiol	2.5 - 250
17β-Dihydroequilin	5 - 250
17β-$\Delta^{8,9}$-Dehydroestradiol	5 - 250

The CE inter-day coefficient of variation (%CV) and the mean bias for the low, mid, and high quality control samples are summarized below for Study 0713D2-119-US (from *bioanalytical report*) on the next page.

MPA for (Study 0713D2-119-US)

Plasma samples that have been adequately stored frozen at -20° were assayed via a validated radioimmunoassay (RIA) Calibration standards were analyzed from the lower limit of quantitation, . The inter-assay coefficients of variation of the quality control samples for the analytical runs ranged from 7.8% to 10.9%.

Analyte	QC	-------Unconjugated---- % CV	% Bias	----------Total--------- % CV	% Bias
Estrone	Low	10.9	0.7	11.0	-0.7
	Mid	6.2	-1.8	7.5	-4.0
	High	7.7	-0.6	6.8	-3.9
Equilin	Low	9.3	-6.7	10.3	-10.3
	Mid	7.3	-8.0	11.0	-11.5
	High	8.7	-7.9	7.6	-10.2
$\Delta^{8,9}$-Dehydroestrone	Low	9.8	-2.7	10.7	-2.7
	Mid	5.3	-5.6	11.6	-6.9
	High	6.5	-6.0	6.1	-8.0
17β-Estradiol	Low	11.7	-5.9	10.9	-9.5
	Mid	6.3	0.4	10.6	-0.4
	High	7.2	2.5	5.4	2.0
17β-Dihydroequilin	Low	8.0	-5.3	10.3	-6.7
	Mid	5.3	-4.1	11.0	-5.3
	High	6.1	-3.5	5.2	-5.0
17β-$\Delta^{8,9}$-Dehydroestradiol	Low	10.1	-0.7	15.8	1.3
	Mid	7.4	-2.8	12.3	-4.5
	High	7.3	-2.5	7.3	-3.0

For the analysis of total estrone, equilin, $\Delta^{8,9}$ dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol, additional control samples (n = 3) containing their sulfates (except for 17β-dihydroequilin, which was not available at the time of analysis) were analyzed along with the samples. These control samples (designated as QA samples) were used to verify that the hydrolysis of the conjugated estrogens was complete. Although 17β-dihydroequilin sulfate was not included in the QA samples, total concentrations of 17β-dihydroequilin are reported since there is no reason to believe that the enzyme would not

(Revised: 06-MAY-1998)

The CE inter-day coefficient of variation (%CV) and the mean bias for the low, mid, and high quality control samples are summarized below for Study 0713D2-120-US (from *study report and bioanalytical report*).

TABLE 6.5.2.1A. INTERDAY COEFFICIENT OF VARIATION (% CV) AND MEAN BIAS

		-----Unconjugated-----		----------Total---------	
Analyte	QC	% CV	% Bias	% CV	% Bias
Estrone	Low	10.5	-6.7	9.5	-12.7
	Mid	6.0	-3.3	6.2	-1.7
	High	6.9	-0.6	4.5	-0.4
Equilin	Low	3.9	-1.0	6.3	-1.7
	Mid	4.1	-2.5	4.4	-2.0
	High	5.1	-1.0	4.5	-0.1
$\Delta^{8,9}$-Dehydroestrone	Low	7.1	4.7	7.4	8.7
	Mid	5.0	0.4	5.1	3.3
	High	7.0	0.0	6.7	3.0
17β-Estradiol	Low	9.5	7.2	8.3	2.5
	Mid	4.3	3.4	6.0	3.4
	High	6.1	5.0	4.5	7.0
17β-Dihydroequilin	Low	4.7	-3.3	7.3	-3.3
	Mid	3.5	-3.5	3.6	-1.9
	High	4.2	-2.5	4.4	-2.0
17β-$\Delta^{8,9}$-Dehydroestradiol	Low	4.6	2.7	5.6	4.0
	Mid	3.9	-2.1	4.4	-0.3
	High	5.8	-1.5	4.8	1.0

Study 0713D2-120-US:

Analyte	Standard curve range, pg/mL
Estrone	5 - 1000
Equilin	10 - 1000
$\Delta^{8,9}$-Dehydroestrone	5 - 250
17β-Estradiol	2.5 - 250
17β-Dihydroequilin	5 - 250
17β-$\Delta^{8,9}$-Dehydroestradiol	5 - 250

MPA for (Study 0713D2-120-US)

Plasma samples that have been adequately stored frozen at -20°C were assayed via a . Calibration standards were analyzed from the lower limit of quantitation, The interassay coefficients of variation of the quality control samples for the analytical runs ranged from 6.3% to 7.8%.

Attachment 3

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Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.3.1A. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED ESTROGENS FOR ALL DOSE GROUPS IN 119 AND 120 STUDIES (MEAN ± SD)

Component	Dose (mg)	C_{max} (pg/mL)	AUC_t (pg•h/mL)	AUC (pg•h/mL)
Estrone	0.6	80.1 ± 27.0	2837 ± 1043	5209 ± 2467
	0.9	90.3 ± 27.2	3467 ± 1076	6076 ± 2870
	1.25	140.8 ± 56.3	4590 ± 1480	7192 ± 2904
Estrone adjusted for baseline	0.6	57.0 ± 25.0	1229 ± 548	1448 ± 650
	0.9	65.4 ± 24.6	1679 ± 688	2029 ± 982
	1.25	116.3 ± 56.0	2828 ± 1157	3285 ± 1413
Equilin	0.6	30.4 ± 13.5	302 ± 160	621 ± 360
	0.9	34.5 ± 13.9	489 ± 267	843 ± 405
	1.25	56.3 ± 29.0	778 ± 389	1080 ± 485
17β-Estradiol	0.6	11.6 ± 3.8	443 ± 199	845 ± 475
	0.9	14.2 ± 6.0	631 ± 336	1073 ± 690
	1.25	19.7 ± 8.7	777 ± 375	1295 ± 1093
17β-Estradiol adjusted for baseline	0.6	8.5 ± 3.4	227 ± 90	301 ± 123
	0.9	9.8 ± 3.7	317 ± 127	421 ± 198
	1.25	15.5 ± 7.9	477 ± 159	595 ± 226
17β-Dihydroequilin	0.6	24.1 ± 8.7	391 ± 147	521 ± 170
	0.9	29.6 ± 9.8	606 ± 235	775 ± 274
	1.25	48.3 ± 21.3	878 ± 330	1061 ± 384
$\Delta^{8,9}$ –Dehydroestrone	0.6	NA[a]	NA	NA
	0.9	6.1 ± 1.4	NA	NA
	1.25	7.7 ± 2.6	78 ± 85	NA
17β- $\Delta^{8,9}$ – Dehydroestradiol	0.6	7.5 ± 1.9	58 ± 29	NA
	0.9	9.5 ± 3.0	119 ± 77	NA
	1.25	13.8 ± 5.6	200 ± 114	NA

a: NA: Not available due to low plasma concentrations

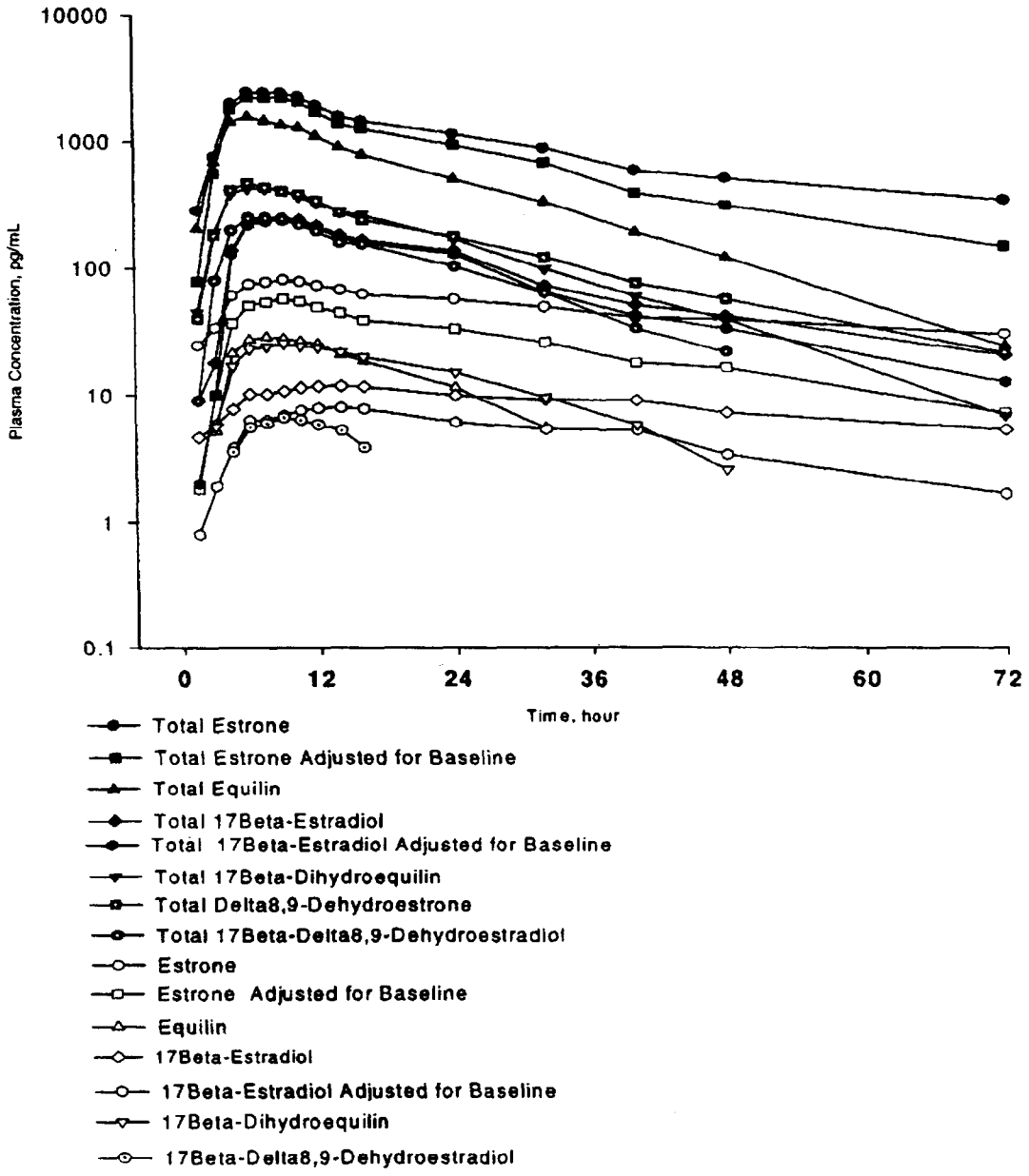
Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.3.1B. PHARMACOKINETIC PARAMETERS FOR TOTAL ESTROGENS AND MPA FOR ALL DOSE GROUPS IN 119 AND 120 STUDIES
(MEAN ± SD)

Component	Dose (mg)	C_{max} (ng/mL)	AUC_t (ng•h/mL)	AUC (ng•h/mL)
Estrone	0.6	2.45 ± 0.84	49.6 ± 19.8	61.2 ± 27.9
	0.9	2.86 ± 1.13	65.8 ± 24.3	78.3 ± 27.6
	1.25	4.56 ± 1.77	93.3 ± 36.6	108.2 ± 39.5
Estrone adjusted for baseline	0.6	2.28 ± 0.79	37.7 ± 14.0	41.0 ± 16.0
	0.9	2.63 ± 1.07	48.9 ± 17.6	53.4 ± 20.5
	1.25	4.34 ± 1.71	77.2 ± 29.8	84.2 ± 34.2
Equilin	0.6	1.57 ± 0.65	20.9 ± 9.1	22.3 ± 9.3
	0.9	1.82 ± 0.80	28.6 ± 13.9	30.4 ± 14.5
	1.25	3.03 ± 1.18	42.3 ± 22.0	44.1 ± 22.7
17β-Estradiol	0.6	0.25 ± 0.13	3.99 ± 1.41	4.70 ± 1.64
	0.9	0.33 ± 0.17	6.27 ± 1.87	7.11 ± 2.12
	1.25	0.51 ± 0.30	7.92 ± 2.56	8.80 ± 2.82
17β-Estradiol adjusted for baseline	0.6	0.24 ± 0.13	3.48 ± 1.31	3.88 ± 1.46
	0.9	0.32 ± 0.17	5.54 ± 1.85	6.03 ± 2.00
	1.25	0.50 ± 0.30	7.22 ± 2.43	7.71 ± 2.53
17β-Dihydroequilin	0.6	0.39 ± 0.15	5.41 ± 2.20	6.03 ± 2.28
	0.9	0.54 ± 0.26	8.96 ± 4.11	9.75 ± 4.27
	1.25	0.81 ± 0.34	12.17 ± 6.19	13.02 ± 6.54
$\Delta^{8,9}$-Dehydroestrone	0.6	0.46 ± 0.14	7.30 ± 2.46	8.16 ± 2.54
	0.9	0.50 ± 0.17	9.46 ± 3.17	10.53 ± 3.39
	1.25	0.79 ± 0.28	13.61 ± 5.02	14.75 ± 5.28
17β-$\Delta^{8,9}$-Dehydroestradiol	0.6	0.18 ± 0.06	2.79 ± 1.02	3.49 ± 1.07
	0.9	0.32 ± 0.22	5.28 ± 2.93	6.05 ± 3.03
	1.25	0.45 ± 0.30	6.91 ± 4.14	7.74 ± 4.23
MPA	3.0	1.19 ± 0.48	22.5 ± 8.7	31.1 ± 10.6
	5.0	2.04 ± 1.13	38.7 ± 14.9	50.1 ± 21.4

Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

Figure 6.1.3.1A Mean Estrogen Plasma Concentrations in All Postmenopausal Women Receiving 2 x 0.45 mg/1.5 mg CE/MPA Tablets



Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.3.1C. UNCONJUGATED ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG/1.5 MG CE/MPA ADMINISTRATION

Component	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	90.9 ± 26.7	9.8 ± 4.6	48.9 ± 13.5	5786 ± 2423
Estrone adjusted for baseline	67.2 ± 24.5	9.8 ± 4.6	21.5 ± 10.5	2042 ± 1063
Equilin	35.1 ± 13.9	8.5 ± 2.9	16.4 ± 8.1	825 ± 367
17β-Estradiol	14.2 ± 5.8	14.5 ± 7.3	44.0 ± 21.8	1003 ± 600
17β-Estradiol adjusted for baseline	10.3 ± 3.7	14.5 ± 7.3	25.5 ± 17.3	425 ± 198
17β-Dihydroequilin	29.6 ± 9.4	9.7 ± 3.5	15.0 ± 5.3	762 ± 266
$\Delta^{8,9}$-Dehydroestrone	5.8 ± 0.9	6.8 ± 1.5	NA[a]	NA
17β-$\Delta^{8,9}$-Dehydroestradiol	9.3 ± 2.5	9.0 ± 3.3	NA	NA

a: NA = Not available due to low plasma concentrations

TABLE 6.1.3.1D. TOTAL ESTROGEN AND MPA PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG/1.5 MG CE/MPA ADMINISTRATION

Component	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.97 ± 1.09	8.2 ± 3.2	25.9 ± 6.0	78.3 ± 30.6
Estrone adjusted for baseline	2.76 ± 1.04	8.2 ± 3.2	16.9 ± 6.1	55.9 ± 22.0
Equilin	1.85 ± 0.77	7.2 ± 2.4	12.2 ± 3.1	31.1 ± 15.5
17β-Estradiol	0.33 ± 0.17	10.1 ± 4.8	20.3 ± 6.1	7.0 ± 2.2
17β-Estradiol adjusted for baseline	0.33 ± 0.17	10.1 ± 4.8	16.5 ± 7.1	6.0 ± 1.9
17β-Dihydroequilin	0.53 ± 0.26	8.0 ± 3.4	12.4 ± 3.9	9.5 ± 4.3
$\Delta^{8,9}$-Dehydroestrone	0.53 ± 0.16	7.0 ± 2.3	17.6 ± 3.7	10.9 ± 3.4
17β-$\Delta^{8,9}$-Dehydroestradiol	0.30 ± 0.25	8.4 ± 3.3	13.9 ± 3.9	5.8 ± 2.9
MPA	1.19 ± 0.47	2.7 ± 1.4	47.2 ± 19.4	32.0 ± 11.4

Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.3.1E. UNCONJUGATED ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.3 MG/1.5 MG CE/MPA ADMINISTRATION

Component	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	78.7 ± 27.7	9.4 ± 8.1	51.3 ± 15.5	5029 ± 2269
Estrone adjusted for baseline	55.9 ± 25.7	9.4 ± 8.1	19.8 ± 7.7	1429 ± 703
Equilin	30.0 ± 13.0	7.9 ± 3.3	14.0 ± 10.5	590 ± 250
17β-Estradiol	11.3 ± 3.8	12.8 ± 9.1	51.1 ± 32.9	833 ± 493
17β-Estradiol adjusted for baseline	8.3 ± 3.0	12.8 ± 9.1	21.8 ± 9.8	300 ± 136
17β-Dihydroequilin	23.9 ± 9.0	8.0 ± 3.3	13.9 ± 4.1	528 ± 172
$\Delta^{8,9}$-Dehydroestrone	NA	NA	NA	NA
17β-$\Delta^{8,9}$-Dehydroestradiol	7.5 ± 1.9	7.4 ± 2.2	NA	NA

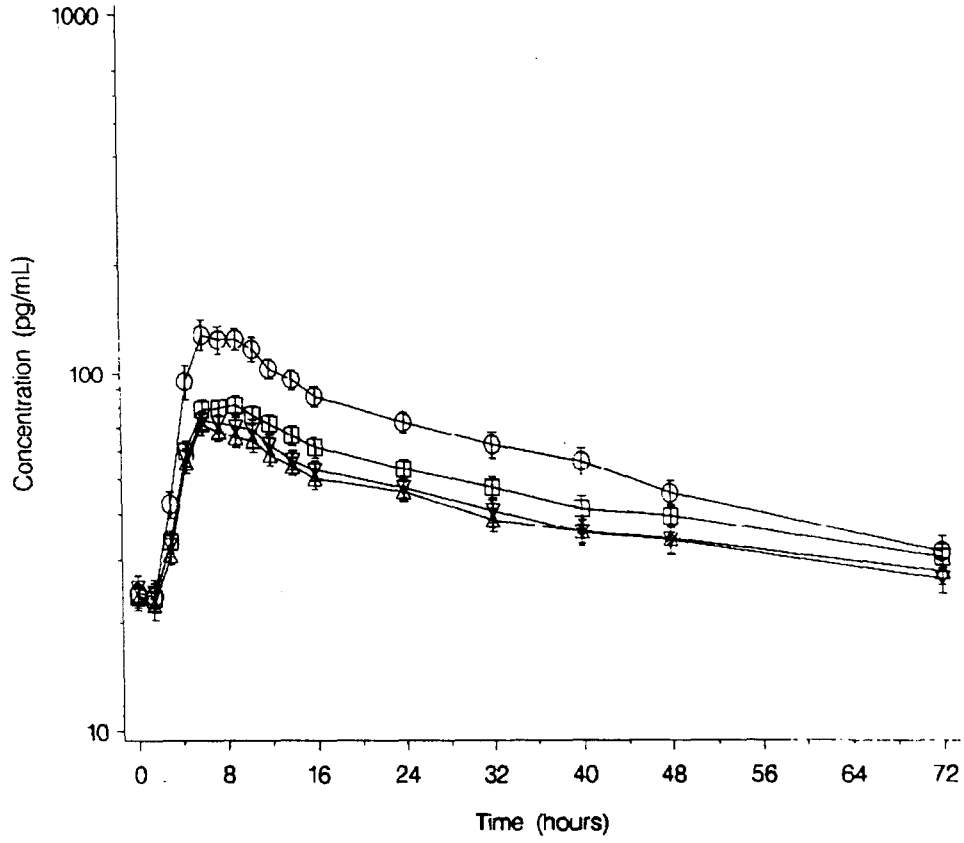
a:NA = Not available due to low plasma concemtrations

TABLE 6.1.3.1F. TOTAL ESTROGEN AND MPA PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.3 MG/1.5 MG CE/MPA ADMINISTRATION

Component	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.37 ± 0.87	7.1 ± 1.9	26.5 ± 8.7	61.5 ± 30.0
Estrone adjusted for baseline	2.20 ± 0.83	7.1 ± 1.9	16.3 ± 5.2	41.2 ± 17.6
Equilin	1.54 ± 0.66	5.5 ± 1.6	11.5 ± 2.8	22.2 ± 9.3
17β-Estradiol	0.24 ± 0.12	8.7 ± 3.8	21.0 ± 7.6	4.6 ± 1.7
17β-Estradiol adjusted for baseline	0.24 ± 0.12	8.7 ± 3.8	16.0 ± 5.2	3.8 ± 1.5
17β-Dihydroequilin	0.39 ± 0.17	6.3 ± 2.8	11.3 ± 2.9	6.0 ± 2.3
$\Delta^{8,9}$-Dehydroestrone	0.45 ± 0.16	6.1 ± 1.6	16.4 ± 3.3	8.1 ± 2.7
17β-$\Delta^{8,9}$-Dehydroestradiol	0.18 ± 0.07	7.9 ± 2.6	13.4 ± 3.7	3.5 ± 1.1
MPA	1.20 ± 0.52	2.8 ± 1.7	42.3 ± 14.2	29.4 ± 8.7

FIG. 5 MEAN +/- SE UNCONJUGATED ESTRONE PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

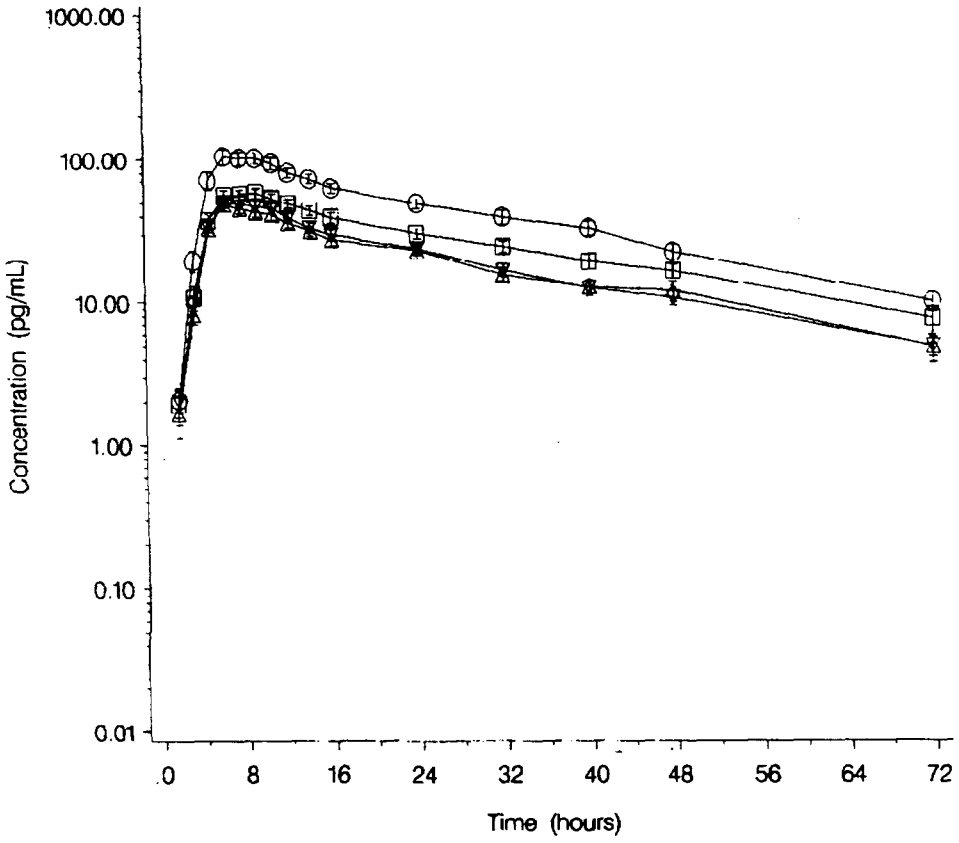
Figure 5
Mean +/− SE
Unconjugated Estrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 13 MEAN +/- SE UNCONJUGATED ESTRONE PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: DIFFERENT PREMARIN AND MPA FORMULATIONS

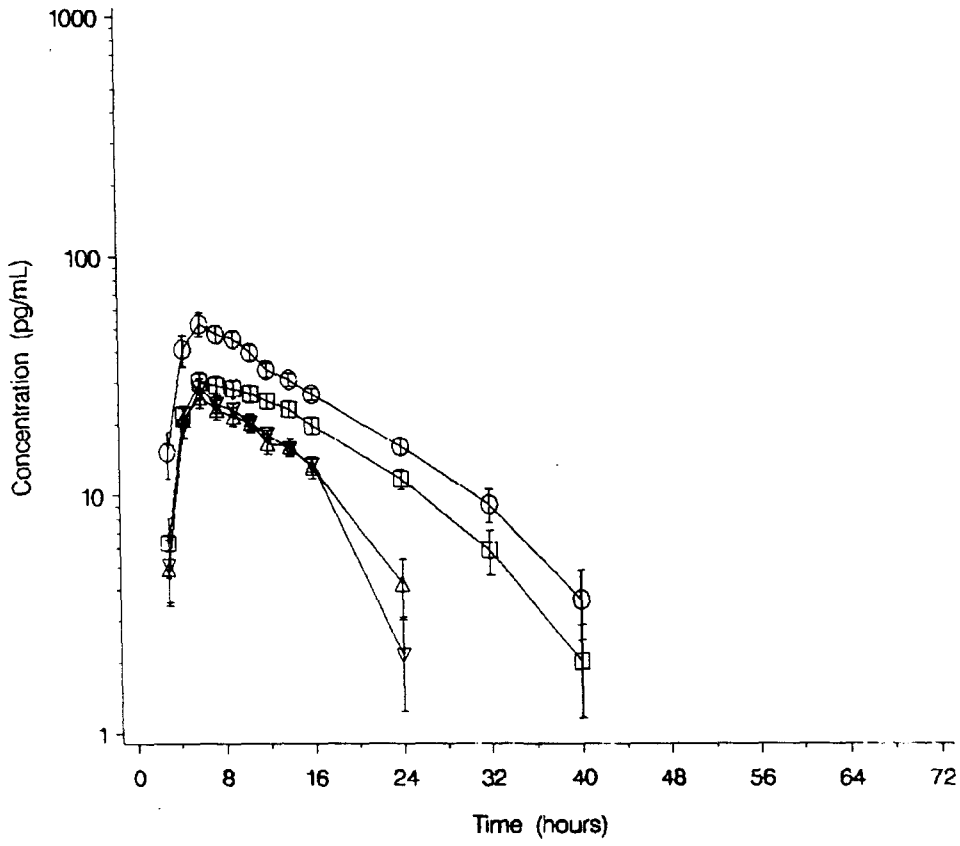
Figure 13
Mean +/− SE
Unconjugated Estrone Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 21 MEAN +/- SE UNCONJUGATED EQUILIN PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

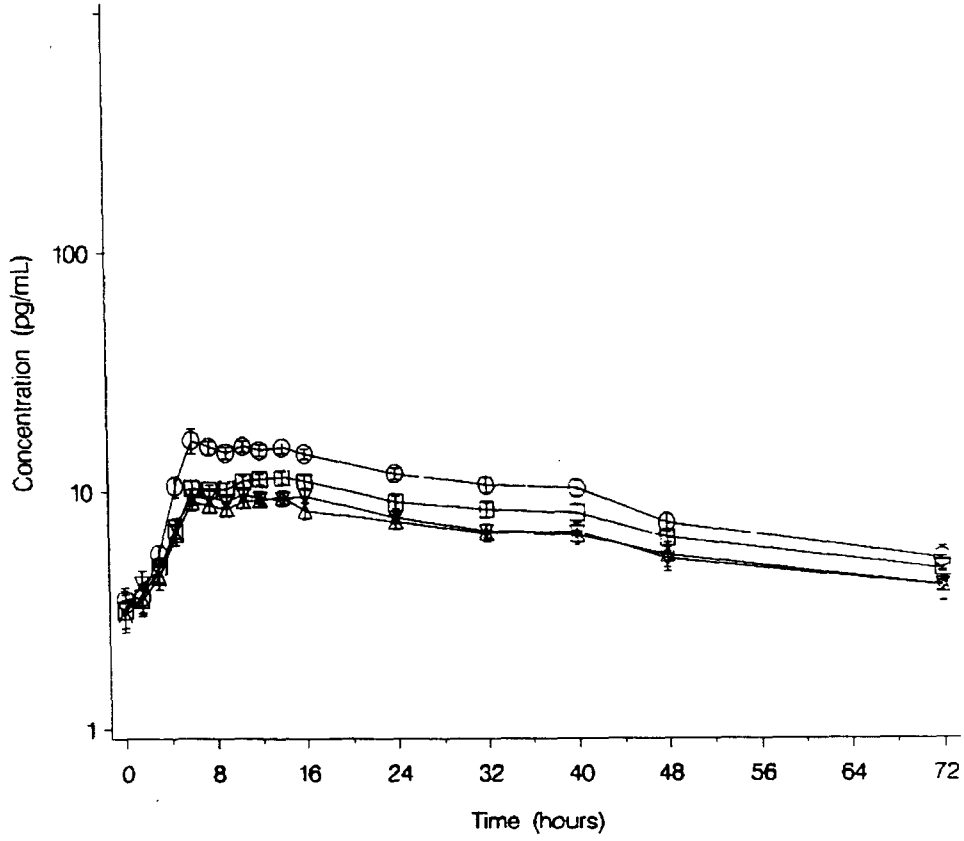
Figure 21
Mean +/− SE
Unconjugated Equilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 29 MEAN +/- SE UNCONJUGATED 17BETA-ESTRADIOL PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

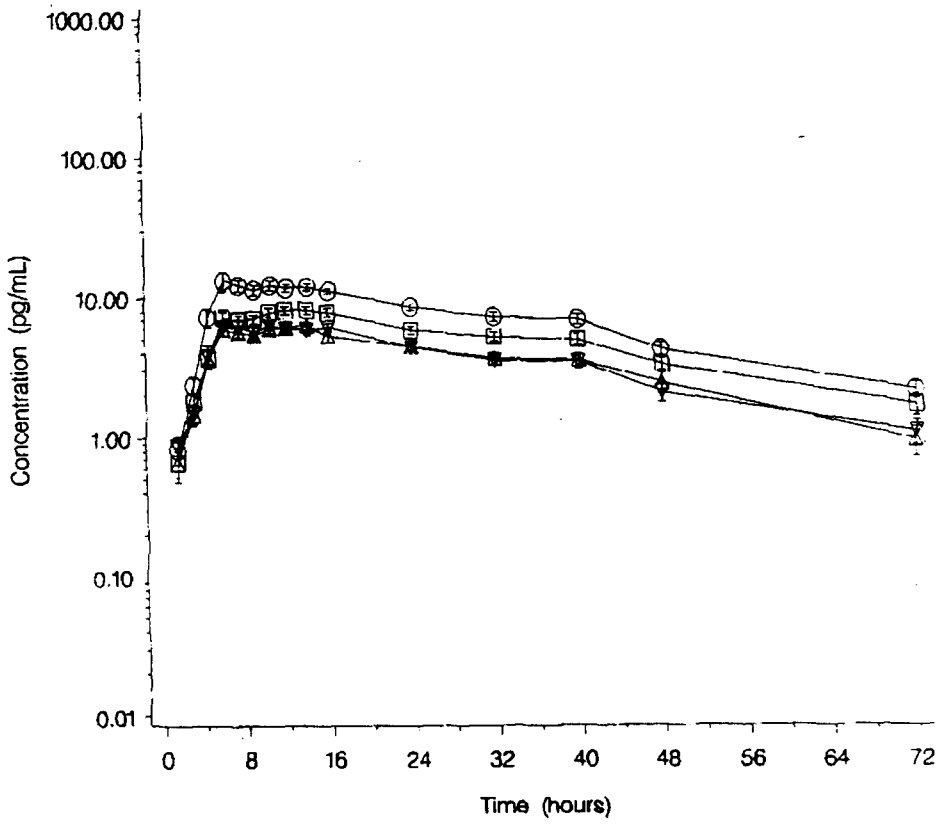
Figure 29
Mean +/- SE
Unconjugated 17Beta-Estradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2-120-US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 37 MEAN +/- SE UNCONJUGATED 17BETA-ESTRADIOL PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: DIFFERENT PREMARIN AND MPA FORMULATIONS

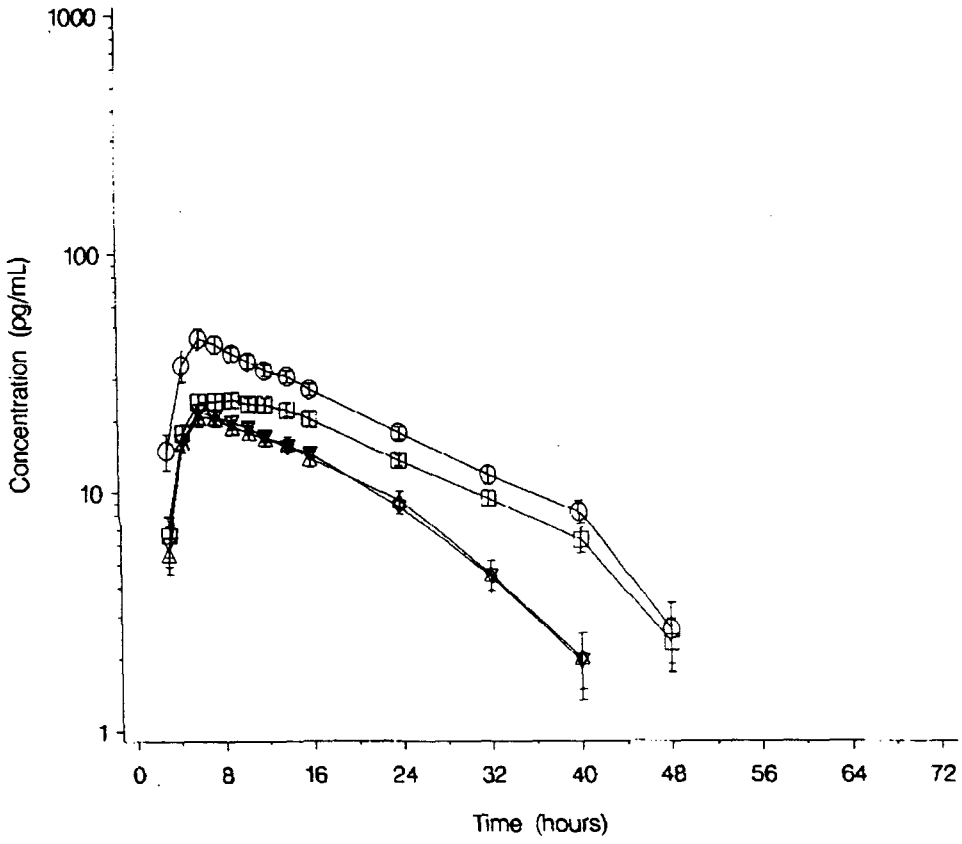
Figure 37
Mean +/− SE
Unconjugated 17Beta−Estradiol Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 45 MEAN +/- SE UNCONJUGATED 17BETA-DIHYDROEQUILIN PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

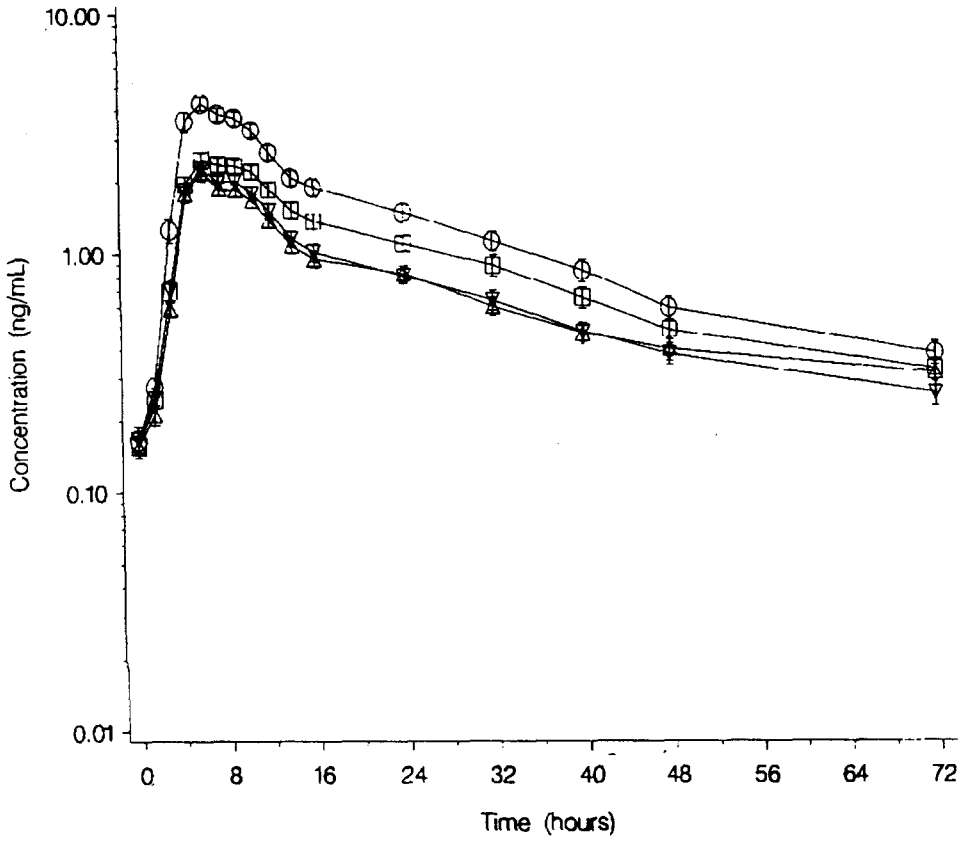
Figure 45
Mean +/− SE
Unconjugated 17Beta−Dihydroequilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 64 MEAN +/- SE TOTAL ESTRONE PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

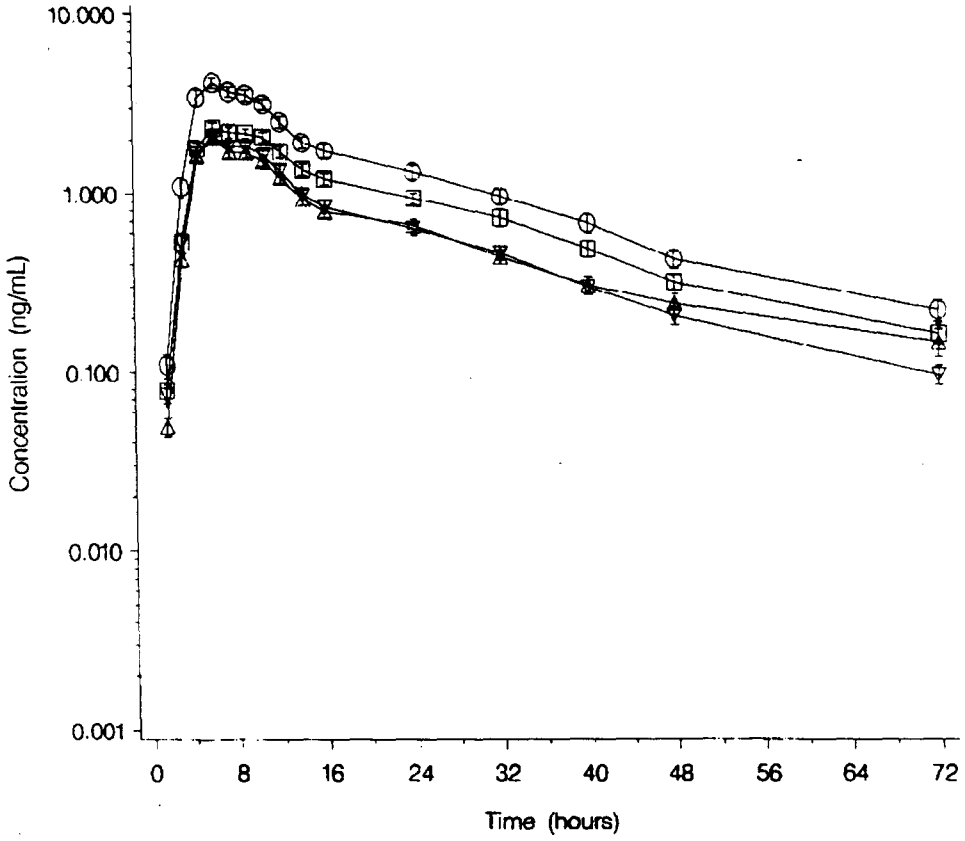
Figure 64
Mean +/− SE
Total Estrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 72 MEAN +/- SE TOTAL ESTRONE PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE : DIFFERENT PREMARIN AND MPA FORMULATIONS

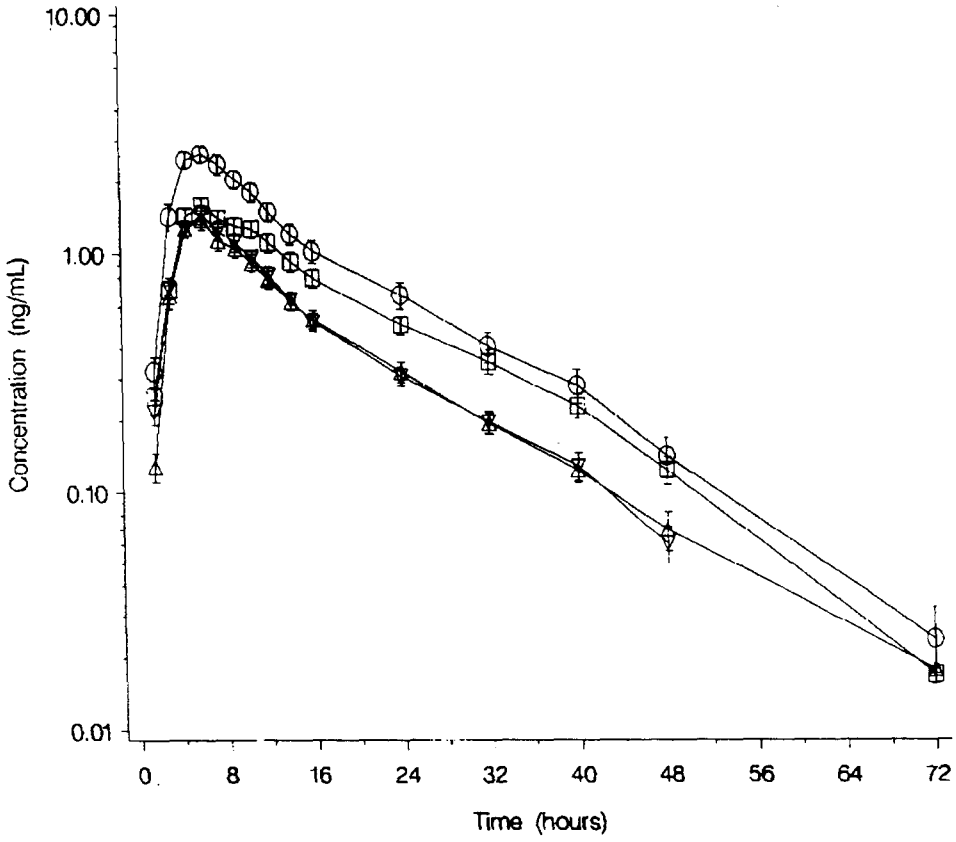
Figure 72
Mean +/- SE
Total Estrone Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2-120-US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 80 MEAN +/- SE TOTAL EQUILIN PLASMA CONCENTRATIONS: - DIFFERENT PREMARIN AND MPA FORMULATIONS

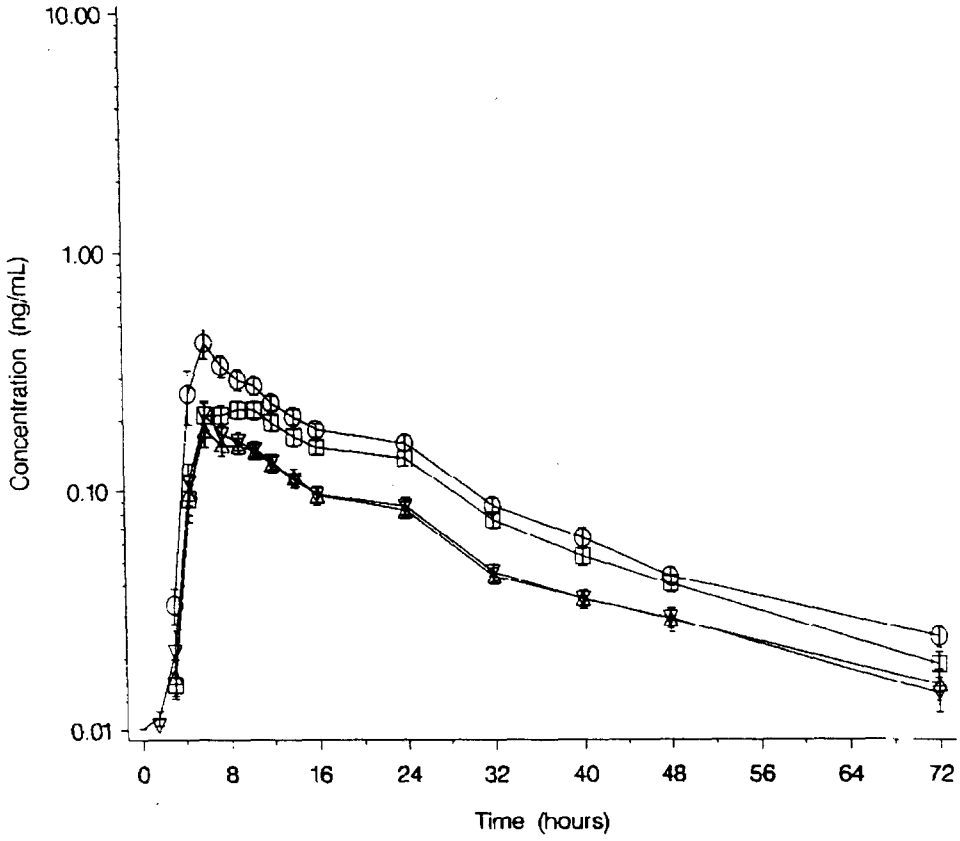
Figure 80
Mean +/− SE
Total Equilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 88 MEAN +/- SE TOTAL 17BETA-ESTRADIOL PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

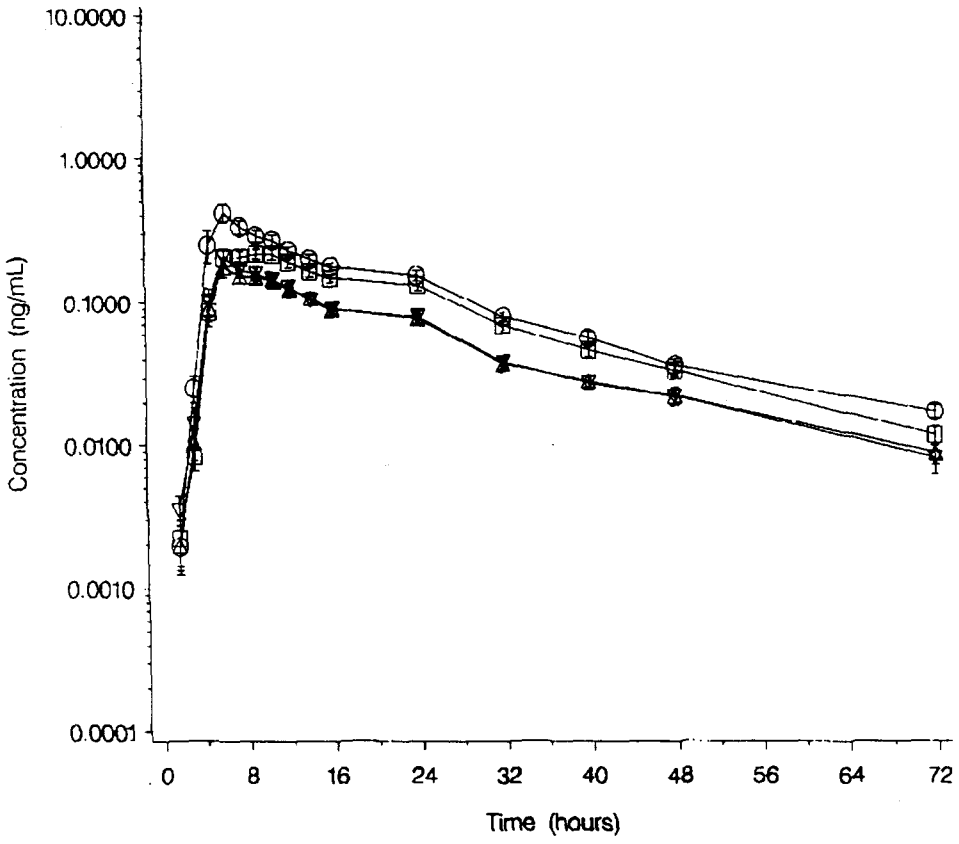
Figure 88
Mean +/− SE
Total 17Beta−Estradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 96 MEAN +/- SE TOTAL 17BETA-ESTRADIOL PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: DIFFERENT PREMARIN AND MPA FORMULATIONS

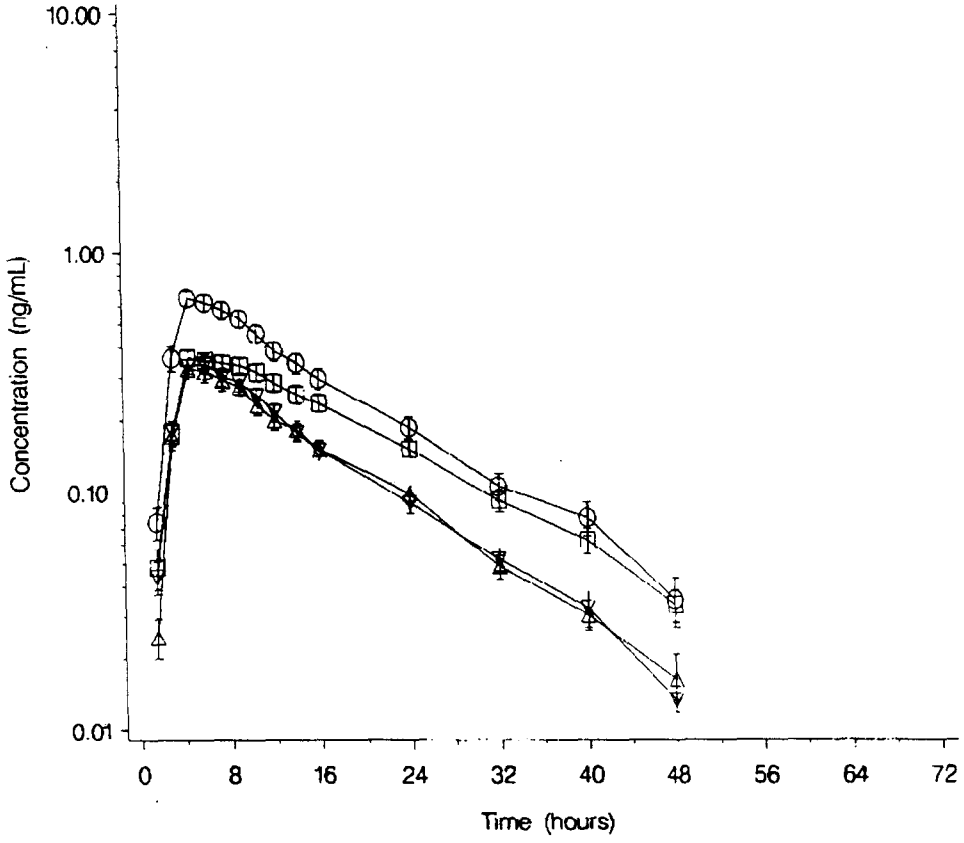
Figure 96
Mean +/− SE
Total 17Beta−Estradiol Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 104 MEAN +/- SE TOTAL 17BETA-DIHYDROEQUILIN PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

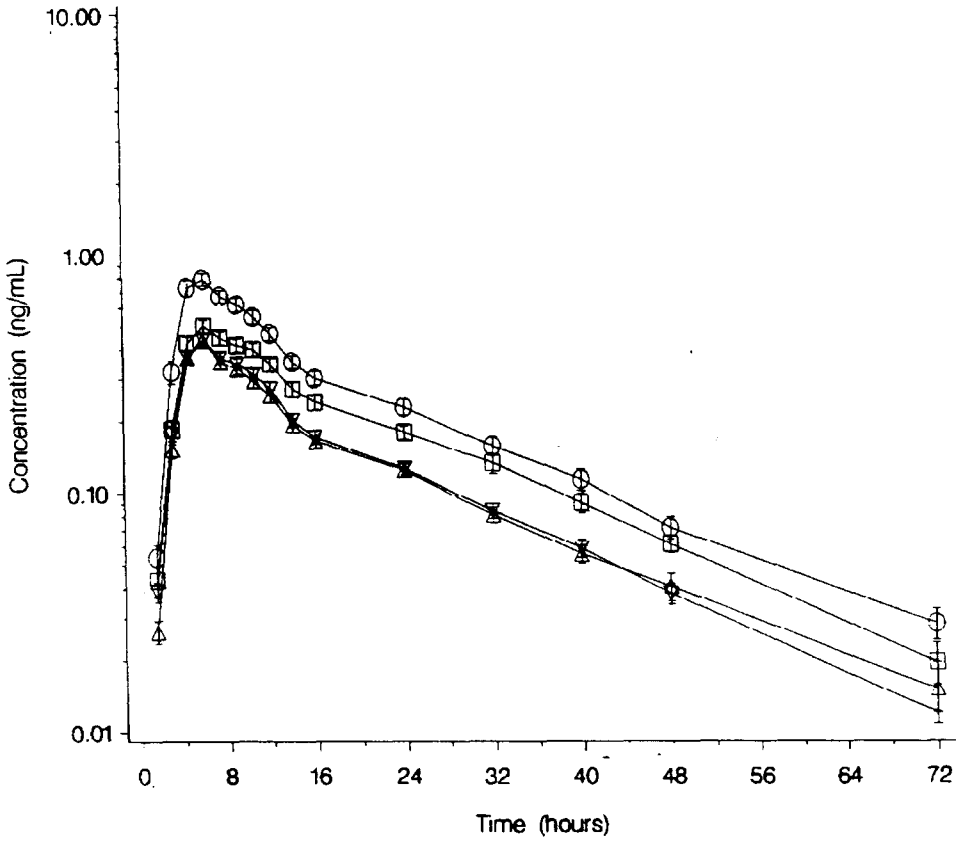
Figure 104
Mean +/- SE
Total 17Beta-Dihydroequilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2-120-US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 112 MEAN +/ SE TOTAL DELTA8,9-DEHYDROESTRONE PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

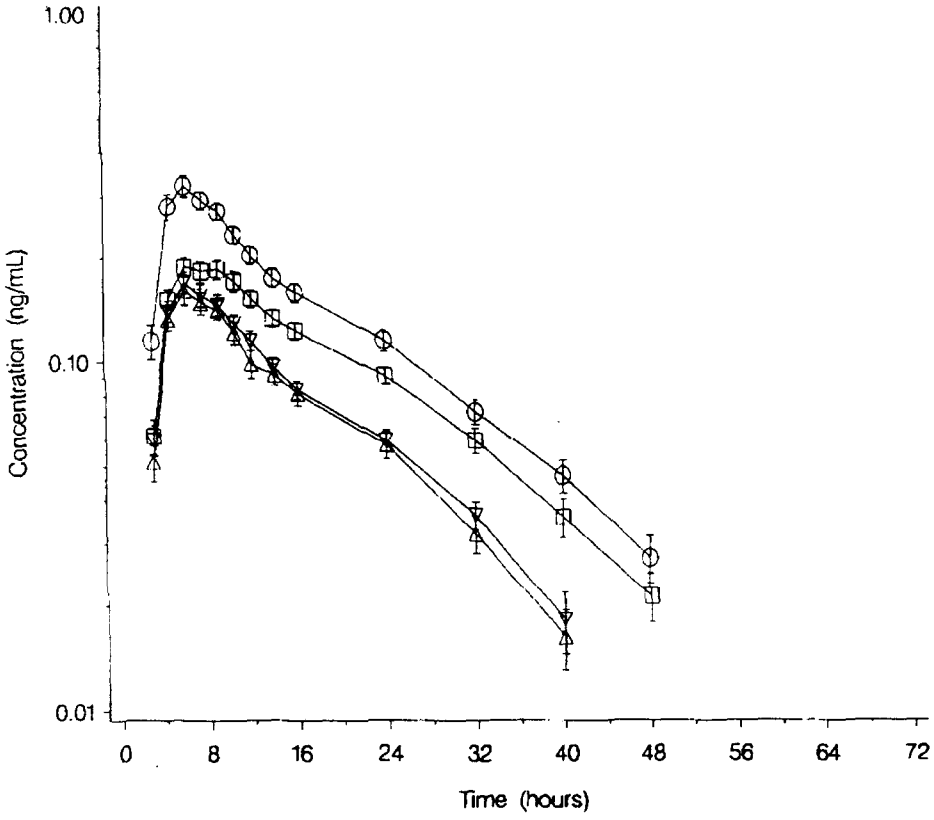
Figure 112
Mean +/− SE
Total Delta8,9−Dehydroestrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 120 MEAN +/- SE TOTAL 17BETA-DELTA8,9-DEHYDROESTRADIOL PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

Figure 120
Mean +/- SE
Total 17Beta-Delta8,9-Dehydroestradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2-120-US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets
△ Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
▽ Two Premarin 0.30 mg Tablets

FIG. 126 MPA PLASMA CONCENTRATIONS: TWO PREMARIN
- · 0.30 MG/MPA 1.5 MG COMBINATION TABLETS

Figure 126
MPA Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg/MPA 1.5 mg Combination Tablets
Protocol 0713D2-120-US

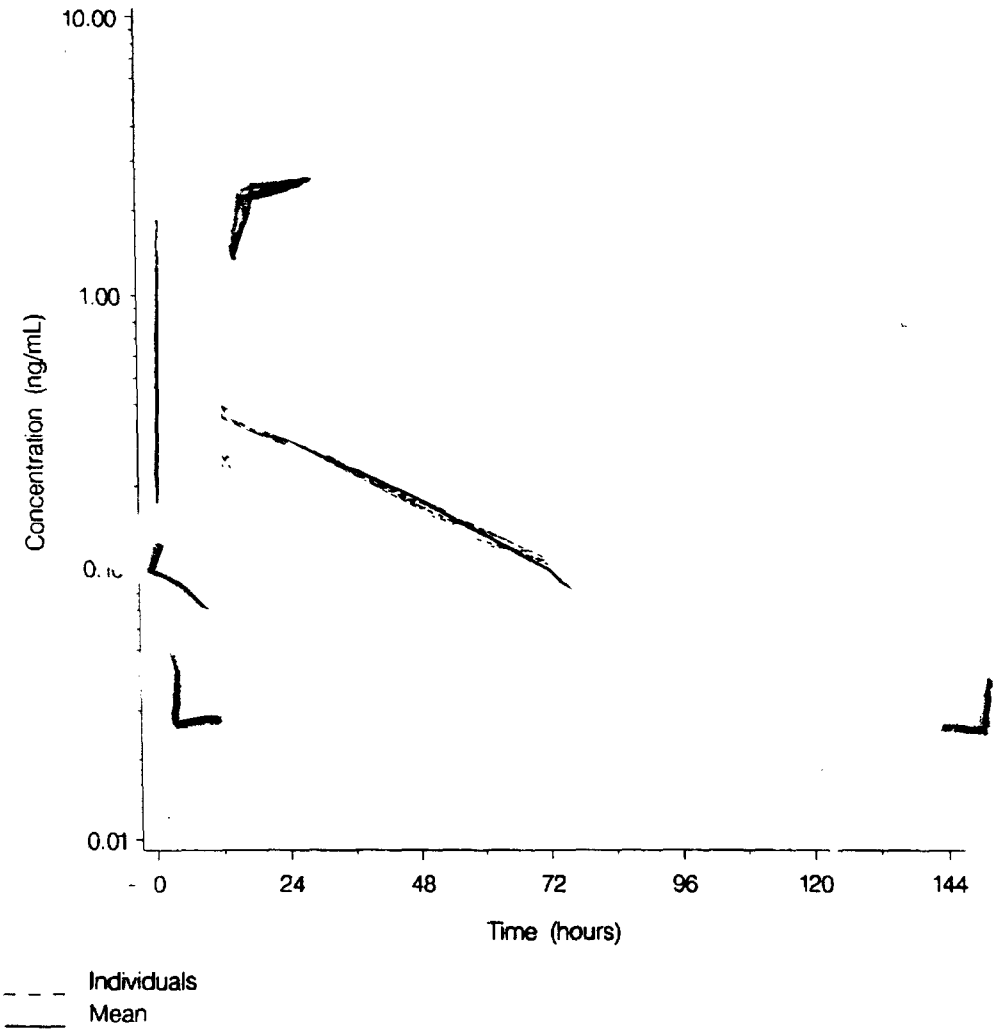
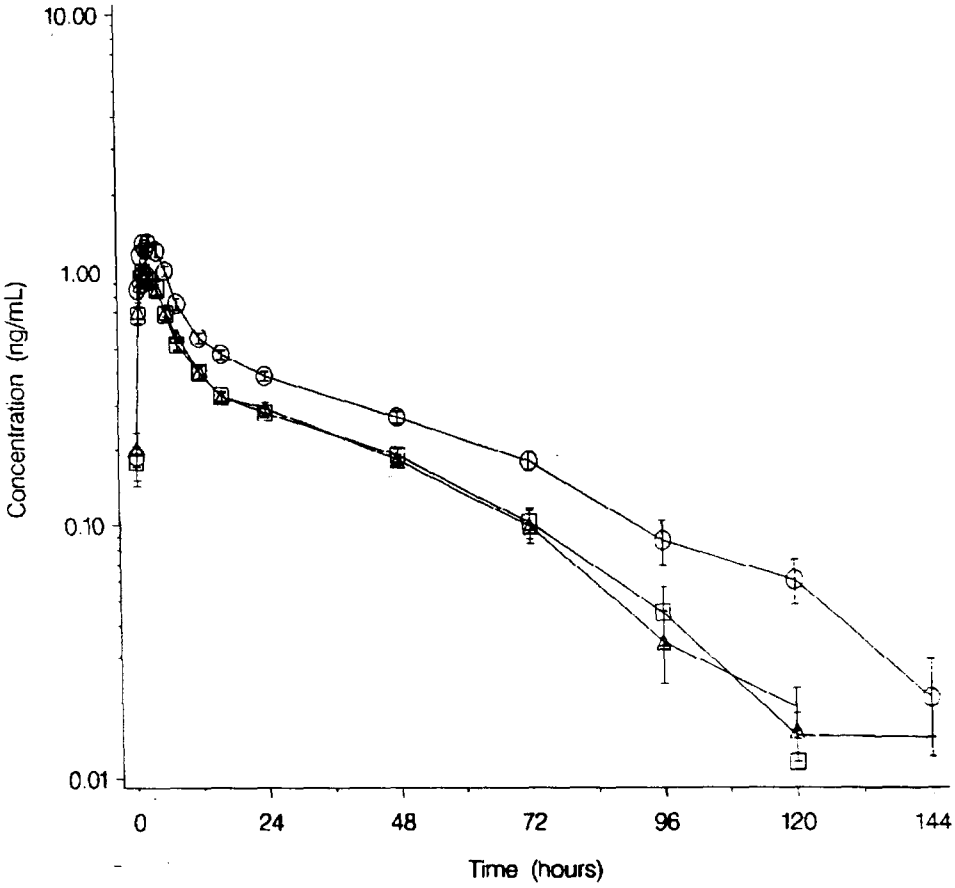


FIG. 127 MEAN +/- SE MPA PLASMA CONCENTRATIONS: DIFFERENT PREMARIN AND MPA FORMULATIONS

Figure 127
Mean +/− SE
MPA Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Different Premarin and MPA Formulations
Protocol 0713D2−120−US



○ Two Premarin 0.625 mg/MPA 2.5 mg Combination Tablets
□ Two Premarin 0.45 mg/MPA 2.5 mg Combination Tablets
△ Two Premarin 0.45 mg/MPA 1.5 mg Combination Tablets

Attachment 4

APPEARS THIS WAY
ON ORIGINAL

Table 3.2 Premarin And MPA Treatments From -119 And -120 Studies

Study	Treatment
119 and 120	Two Premarin 0.625 mg/MPA 2.5 mg® tablets (combination-tablet formulation)
119	Two [redacted] tablets (combination-tablet formulation)
119 and 120	Two Premarin 0.45 mg/MPA 1.5 mg tablets (combination-tablet formulation)
120	Two Premarin 0.30 mg/MPA 1.5 mg tablets (combination-tablet formulation)
119	Two Premarin 0.45 mg tablets
120	Two Premarin 0.30 mg tablets

The following statistical model was applied to these data:

$$Y_{ijk} = \mu + STUDY_i + SUB_{j(i)} + DOSE_k \qquad (3)$$

where,

μ	= grand mean
$STUDY_i$	= i^{th} study; i = 119 or 120
$SUB_{j(i)}$	= j^{th} subject nested within the i^{th} study;j = 1,..,31
$DOSE_k$	= k^{th} dose; k = 1,..,3 for Premarin and k= 1,2 for MPA

Prior to statistical comparisons, the dose-dependent parameters C_{max}, AUC_t, and AUC were normalized to the lowest Premarin or MPA dose. Statistical comparisons were not performed on the endogenous estrogens (unconjugated and total estrone and 17β-estradiol) prior to baseline adjustment. The SAS statistical software package was used for all statistical analyses.[2]

Dose proportionality was assessed by using the 'power model' of Gough et al.[3] The 'power model' is based on the assumption of a linear relationship between the log (measured pharmacokinetic parameter) and log (dose), which upon exponentiation yields the relationship:

$$y_{ij} = \alpha \bullet (D_j)^{\beta} \qquad (4)$$

In Equation 4, y_{ij} represents a measured dose-dependent parameter (e.g., C_{max}, AUC_t, and AUC) after the jth dose for the ith subject; D_j is the amount of the jth dose; α depends on the subject and error; and β is an indicator of dose proportionality. A log transformation of the data was used to linearize the equation [ie, $\log(y_{ij}) = \log(\alpha) + \beta \bullet \log(D_j)$]. Exact dose proportionality requires that $\beta = 1$ for dose-dependent parameters; for empirical estimates of β, the value of 1 must lie within the confidence interval for β.[3]

4. RESULTS AND DISCUSSION

Two clinical pharmacology studies (-119 and -120) were performed to characterize the pharmacokinetics of conjugated estrogens in lower strength Premarin dosage forms, both when administered alone and in combination with MPA. Six different dosage forms were administered across the two studies. Premarin/MPA dosage forms of 0.625 mg/2.5 mg and 0.45 mg/1.5 mg were administered in both studies. Other combinations of 0.3 and 0.45 mg of Premarin and 1.5 and 2.5 mg of MPA dosage forms were also administered. These dosage forms were selected to complement those being examined in the HOPE clinical trial. Because of the low doses, two tablets were administered in each case to provide plasma concentrations which could be more accurately assayed. This results in Premarin doses of 0.6, 0.9 and 1.25 mg and MPA doses of 1.5 and 3.0 mg. Even with the administration of two tablets, two unconjugated estrogens, $\Delta^{8,9}$-dehydroestrone and 17β - $\Delta^{8,9}$-dehydroestradiol, were measurable in only a minimum number of samples. For these components, limited pharmacokinetic data and statistical parameters are available.

Two estrogen components, estrone and 17β-estradiol, are present as endogenous estrogens in women; pharmacokinetic data are provided for these estrogens on an unadjusted basis and also following an adjustment for baseline concentrations. The parameters obtained following the baseline adjustment computation are utilized for the dose proportionality analysis. All estrogen components, whether from combination dosage forms or Premarin-alone administration, are included in the dose proportionality analysis, due to their similar formulation characteristics. The number of observations available for each parameter is reported in the Supportive Tables.

The pharmacokinetic parameters of the estrogen components and MPA in healthy postmenopausal women receiving the different Premarin and MPA doses are presented in Supportive Tables 1-17. The statistical analysis for each pharmacokinetic parameter demonstrate that there was not a significant difference across studies for any component

Table 4.3 Dose Proportionality Analysis For Estrogen Components And MPA

Component	Pharmacokinetic Parameter	95% Confidence Limit for Exponent of Power Model
Unconjugated Estrone Adjusted for Baseline	C_{max}	0.729-1.135
	AUC_t	0.926-1.375
	AUC	0.885-1.350
Unconjugated Equilin	C_{max}	0.588-1.004
	AUC_t	1.058-1.572
	AUC	0.571-1.046
Unconjugated 17β- Estradiol	C_{max}	0.604-0.974
	AUC_t	0.833-1.239
	AUC	0.716-1.161
Unconjugated 17β- Dihydroequilin	C_{max}	0.727-1.077
	AUC_t	0.927-1.301
	AUC	0.797-1.126
Unconjugated 17β- $\Delta^{8,9}$ -Dehydroestradiol	C_{max}	0.616-0.946
	AUC_t	1.251-1.981
	AUC	NA[a]
Total Estrone Adjusted for Baseline	C_{max}	0.621-1.021
	AUC_t	0.766-1.151
	AUC	0.756-1.160
Total Equilin	C_{max}	0.655-1.077
	AUC_t	0.709-1.139
	AUC	0.682-1.097
Total 17β-Estradiol Adjusted for Baseline	C_{max}	0.654-1.173
	AUC_t	0.817-1.228
	AUC	0.764-1.165
Total 17β- Dihydroequilin	C_{max}	0.762-1.168
	AUC_t	0.884-1.304
	AUC	0.822-1.221
Total $\Delta^{8,9}$ – Dehydrocstrone	C_{max}	0.526-0.876
	AUC_t	0.651-1.007
	AUC	0.613-0.948
Total 17β-$\Delta^{8,9}$ - Dehydroestradiol	C_{max}	0.875-1.340
	AUC_t	0.983-1.469
	AUC	0.827-1.244
MPA	C_{max}	0.722-1.195
	AUC_t	0.847-1.272
	AUC	0.697-1.100

a:NA: Not available due to low plasma concentrations

Attachment 5

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text of the annotated and non-annotated draft package inserts for **PREMPRO™** (continuous regimen) and **PREMPHASE™** (sequential regimen). The September 1994 labeling revisions included the addition of a Clinical Pharmacokinetics subsection under Clinical Pharmacology to address the food effect on MPA (as described in the food-effect study No. 713-B-114-US). In addition, key elements of the Division's 1992 Estrogen Labeling Guidance* which are *pertinent to combination estrogen/progestin products* were also incorporated in the labelings.

*This Guidance was published in the Federal Register of June 28, 1994.

On December 8, 1994, Amendment 7 to NDA 20-303 was submitted by the sponsor. In this amendment the sponsor included their responses to the Division of Biopharmaceutics request for additional dissolution and formulation information for the Premarin and research tablets used in the bioequivalence, drug interaction, and food-effect studies.

On December 20, 1994, Amendment 9 to NDA 20-303 was submitted for review. In this amendment the sponsor included additional dissolution data for the bio-batches of currently marketed Premarin, Premarin Research, and the new to-be-marketed Premarin tablets employing the "long dissolution method" that may be published in the March-April 1995 PF, and then in the USP 3rd Supplement of September 1995-effective on November 1995 (i.e., Apparatus 2; paddle, 50 rpm, 900 mL water at 37°C, 12 units, sampling at 2, 5, and 8 hours, and a ——— assay).

Lastly, it should be noted that on January 10, 1994, the sponsor submitted a supplemental application (S-086) to NDA 04-728 for Premarin® tablets which also included the above mentioned comparative bioavailability study No. 713-X-110-US. The bioequivalence study No. 713-X-110-US was reviewed by Mr. John Hunt of the Division of Biopharmaceutics. Overall summary information for study No. 713-X-110-US is included in this review, but the specific reviewing information for study No. 713-X-110-US submitted under NDA 04-728 (S-086) can be found in Attachment IV.

II. RECOMMENDATION:

The Division of Biopharmaceutics has reviewed the original NDA 20-303 which was resubmitted on December 30, 1993 and the four Amendments to this NDA dated July 12, September 14, September 30, December 8, and December 20, 1994 for Conjugated Estrogens and Medroxyprogesterone Tablets.

After review of the analytical and pharmacokinetic information submitted in studies 713-X-110-US, 713-B-103-US, and 713-B-114-US, it is determined that i) the analytical methodologies used for the determination

following single dose administration there was no apparent pharmacokinetic interaction between Premarin and MPA, and iv) food significantly increased the Cmax by 90% and AUC by 30% of MPA from a 2.5 mg tablet and lowered 23-30% the Cmax of the respective estrogens from a 0.625 mg Premarin tablet. Therefore, based upon the review of these data, the Division of Biopharmaceutics believes that the sponsor had provided sufficient information to support the product's approval.

Regarding the proposed package inserts for PREMPRO™ and PREMPHASE™, currently FDA is attempting to standardize the content and presentation of information/data that is to be given in the Pharmacokinetics section of the Clinical Pharmacology section of a product's package insert. Therefore, it is recommended that the package insert's Pharmacokinetics section be reorganized to present appropriate information/data under the subheadings of Absorption, Distribution, Metabolism, and Excretion. Following this, should be two sections with the headings Drug-Drug Interaction and Food-Drug Interaction. Lastly a table with mean (SD) pharmacokinetic parameters to include Tmax, Cmax, Oral Clearance, and half-life for the estrogenic components (i.e., estrone, adjusted estrone, equilin, total estrone, adjusted total estrone, and total equilin) as well as for medroxyprogesterone acetate, should be prepared. For providing mean pharmacokinetic parameter values, all the relevant and appropriate data from across the different studies should be used. The package insert additional information may be obtained from both sponsor's studies and published references. After the pharmacokinetic information is incorporated into the labelings, the sponsor should resubmit the package inserts for review.

Lastly, due to the fact that the interaction between Premarin and MPA was studied under single dose conditions, the Division of Biopharmaceutics feels that additional information following the multiple dosing schedule for the proposed therapies (PREMPRO™ and PREMPHASE™) is needed. Therefore, to determine possible accumulation and potential interaction effects under chronic administration, it is recommended as was previously agreed upon, that in the required Phase IV clinical study, drug blood levels of Premarin components and MPA be determined. Before initiation of the study, it is recommended to discuss the study design and sampling times of the to-be-conducted bio-study with the Division of Biopharmaceutics.

In conclusion, this submission is acceptable, provided the sponsor submits a revised copy of the pharmacokinetic section to be incorporated in the package inserts, and additional Phase IV data are submitted.

Please convey the Recommendation as appropriate to the sponsor.

NOTE: Attachments I to VIII are being retained in the Division of Biopharmaceutics and may be obtained under request.

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Attachment 6

TABLE 8.18A. **UNCONJUGATED** ESTROGEN GEOMETRIC LEAST SQUARES (GLS) MEAN RATIO (0.30 mg PREMARIN/1.5 mg MPA to 0.30 mg PREMARIN) AND 90% CONFIDENCE LIMITS (CL) FOR PHARMACOKINETIC PARAMETERS IN HEALTHY POSTMENOPAUSAL WOMEN RECEIVING TWO 0.30-mg PREMARIN/1.5-mg MPA TABLETS OR TWO 0.30-mg PREMARIN TABLETS

Component	Statistical Test	C_{max}	T_{max}	AUC_t	AUC
Unconjugated Estrone	GLS Mean Ratio[a]	97	106	97	95
	90% CL	89-105	94-120	89-105	88-102
Unconjugated Estrone Adjusted for Baseline	GLS Mean Ratio	95	106	95	95
	90% CL	86-106	94-120	84-107	84-107
Unconjugated Equilin	GLS Mean Ratio	97	105	104	94
	90% CL	88-108	93-120	92-116	81-109
Unconjugated 17β-Estradiol	GLS Mean Ratio	95	115	91	93
	90% CL	87-104	97-135	83-99	83-104
Unconjugated 17β-Estradiol Adjusted for Baseline	GLS Mean Ratio	99	115	96	95
	90% CL	90-109	97-135	85-108	84-108
Unconjugated 17β-Dihydroequilin	GLS Mean Ratio	98	99	99	102
	90% CL	89-107	86-113	91-109	94-111
Unconjugated $\Delta^{8,9}$-Dehydroestrone	GLS Mean Ratio	93	65	-[b]	-[b]
	90% CL	56-156	41-103	-	-
Unconjugated 17β-$\Delta^{8,9}$-Dehydroestradiol	GLS Mean Ratio	95	100	85	-[b]
	90% CL	86-106	85-116	68-105	-

a: x100

b: There were insufficient data to perform statistical analysis.

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TABLE 8.18B. **TOTAL** ESTROGEN GEOMETRIC LEAST SQUARES (GLS) MEAN RATIO (0.30 mg PREMARIN/1.5 mg MPA TO 0.30 mg PREMARIN) AND 90% CONFIDENCE LIMITS (CL) FOR PHARMACOKINETIC PARAMETERS IN HEALTHY POSTMENOPAUSAL WOMEN RECEIVING TWO 0.30-MG PREMARIN/1.5-mg MPA TABLETS OR TWO 0.30-mg PREMARIN TABLETS

Component	Statistical Test	C_{max}	t_{max}	AUC_t	AUC
Total Estrone	GLS Mean Ratio[a]	92	109	95	98
	90% CL	84-101	97-123	88-101	91-105
Total Estrone Adjusted for Baseline	GLS Mean Ratio	92	109	96	98
	90% CL	83-101	97-123	89-103	90-106
Total Equilin	GLS Mean Ratio	95	92	97	98
	90% CL	85-107	82-103	90-105	91-106
Total 17β-Estradiol	GLS Mean Ratio	95	104	92	94
	90% CL	81-110	93-118	82-103	85-104
Total 17β-Estradiol Adjusted for Baseline	GLS Mean Ratio	95	104	94	95
	90% CL	82-111	93-118	84-106	85-105
Total 17β-Dihydroequilin	GLS Mean Ratio	97	107	98	98
	90% CL	87-109	93-123	89-107	90-107
Total $\Delta^{8,9}$-Dehydroestrone	GLS Mean Ratio	96	102	97	98
	90% CL	87-106	93-112	90-104	91-104
Total 17β-$\Delta^{8,9}$-Dehydroestradiol	GLS Mean Ratio	95	112	89	100
	90% CL	87-105	99-125	78-101	93-108

a: x100

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Clinical pharmacology and biopharmaceutics review for Study 713-B-103-US in NDA 20-303 is on the next 2 pages.

One Sided Tests Procedure. Provided also are the arithmetic mean (CV) values for Tmax. The results presented in Table 6 were obtained using an statistical model that assessed the source of variability due to sequence, subject within sequence, treatment, and period. The statistical results indicate that the 90% confidence limits for the pharmacokinetic parameters of the evaluated estrogens were within the 80-125% bioequivalence criteria.

TABLE 6

Component	Tmax[b] Test	Tmax[b] Ref	Cmax 90% CI	AUCT 90% CI	$AUC_{0-\infty}$ 90% CI
Unconjugated					
Estrone	8.9 (30)	8.5 928)	88.9-101.4	94.0-103.2	92.0-103.9
Estrone[a]	8.9 (30)	8.5 928)	87.9-102.6	94.6-108.0	93.5-109.4
Equilin	8.1 (27)	7.6 (31)	85.5-98.8	91.4-105.8	93.7-108.5
Total[c] Estrone	7.5 (29)	7.2 (40)	82.9-96.7	93.3-103.1	91.5-101.8
Total[c] Estrone[a]	7.5 (29)	7.2 (40)	82.6-96.5	93.5-103.3	91.6-102.1
Total[c] Equilin	6.4 (37)	6.1 (32)	81.2-95.9	89.3-100.7	91.2-102.1

a: Adjusted for baseline data.
b: Hours
c:Total = Unconjugated + Conjugated.

COMMENT:

The bioequivalence study (Protocol No. 713-X-110-US) was reviewed by Mr. John Hunt of the Division of Biopharmaceutics (see bio-review in Attachment IV).

2. Study 713-B-103-US, titled "*A Pharmacokinetic of Premarin® and Medroxyprogesterone Acetate Following Concomitant Administration in Postmenopausal Women*", was designed to investigate potential pharmacokinetic interaction between Premarin and medroxyprogesterone acetate (MPA) when given as a combined regimen. This was a single dose, randomized, three period crossover study in which 54 women were enrolled and 52 completed the study. Each subject received single oral doses of Premarin (2 x 0.625 mg) administered alone, MPA (2 x 5 mg encapsulated intact tablets) administered alone, and Premarin tablets and MPA encapsulated tablets administered concomitantly. Blood samples were collected at specific times for 48 hours after administration of Premarin and for 144 hours after administration of MPA. Plasma concentrations of estrone, equilin, total estrone, total equilin, 17β-estradiol, and 17β-dihydroequilin were analyzed by ——— and plasma concentrations of MPA by RIA. Model independent

pharmacokinetic methods were used to analyze the data for each component. Statistical comparisons were made using an analysis of variance with three-period and two levels of residual factor. Analysis of covariance was used for analytes involving baseline. The 90% confidence limits for the pharmacokinetic parameters of estrone, equilin, total estrone, total equilin and MPA (log-transformed data), and the arithmetic mean (CV) values for Tmax are presented in Table 7.

TABLE 7

Component	Tmax		Cmax		AUC0-∞	
	Premarin or MPA	Premarin+MPA (hrs)	Mean Ratio[a] %	90%C.L. %	Mean Ratio[a] %	90%C.L. %
Unconjugated						
Estrone	8.5 (2.2)	8.3 (2.6)	99	(93-105)	97	(93-101)
Estrone[b]	8.5 (2.2)	8.3 (2.6)	98	(91-105)	93	(88-100)
Equilin	7.8 (2.5)	7.2 (2.3)	98	(92-105)	96	(91-101)
Total[c] Estrone	7.0 (2.0)	7.5 (2.1)	100	(92-110)	100	(96-105)
Total[c] Estrone[b]	7.0 (2.0)	7.5 (2.1)	100	(91-109)	99	(94-104)
Total[c] Equilin	5.5 (1.9)	5.9 (1.9)	99	(90-109)	100	(96-104)
MPA	2.7 (1.7)	2.6 (1.7)	87	(80-95)	87	(83-92)

a:Ratio of combination to individual administration.
b:Adjusted for baseline data.
c:Total = Unconjugated + Conjugated.

The results of this study indicate that single dose coadministration of 2x0.625 mg Premarin tablets with 10 mg (2x5 mg encapsulated intact tablets) MPA does not affect the pharmacokinetics of estrone, equilin, total estrone, total equilin, or MPA. In conclusion, the results indicate that there is no pharmacokinetic interaction between Premarin and MPA.

COMMENTS:

1. The originally proposed statistical model (3 RESID levels) was modified to a two levels of residual factor. This modified model is similar to the ANOVA for a collapsed two-period crossover design. The statistical results using the revised and collapsed models were essentially the same. Therefore, this modification of the original model appears to be appropriate

2. The individual data indicates a 13% decrease in Cmax and AUC0-∞ for MPA when MPA is coadministered with Premarin at these single doses. However, the difference in Cmax was not statistically significant.

Attachment 7

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Item 6.1 and Item 8.3.1: Human Pharmacokinetics and Bioavailability Summary

TABLE 6.1.4A FORMULATIONS USED IN CLINICAL STUDIES

	Study		
Component (mg)	119-US	120-US	309-US
CE 0.3		0930329B	0930329B
CE 0.45	0930287B		0930287B
CE 0.625			0929535B
CE 0.3/MPA 1.5		0930328B	0930328B
CE 0.45/MPA1.5	0930288B	0930288B	0930288B
CE 0.45/MPA 2.5	0930289B		0930289B
CE 0.625/MPA 2.5	0930230B	0930230B	0930230B

Table 6.1.4B presents specific batch information for the tablets used in the pharmacokinetic and clinical efficacy studies.

Item 6.1 and Item 8.3.1: **Human Pharmacokinetics and Bioavailability Summary**

TABLE 6.1.4B TABLETS USED IN CLINICAL STUDIES

Component (mg)	Formulation Number	Batch Number	Study	Date of Manufacture
CE 0.3	0930329B	3THP	120-US, 309-US	3/94
		1997B0092	309-US	7/97
CE 0.45	0930287B	3TEL	119-US,	11/93
		1997B00091	309-US	7/97
CE 0.625	0929535B	3TFQ	309-US	5/93
		9610332	309-US	6/96
CE 0.3/MPA 1.5	0930328B	3THN	120-US,	3/94
		1997B0093	309-US	7/97
CE 0.45/MPA	0930288B	3TEM	119-US, 309-US	11/93
		1997B0089	309-US	7/97
CE 0.45/MPA	0930289B	3TEN	119-US,	11/93
		1997B0090	309-US	7/97
CE 0.625/MPA	0930230B	2TQA	119-US,	7/93
		2TPW	309-US	6/93
		2TPT	309-US	5/93
		9610328	309-US	6/96

Formulation details for the batches used in the current clinical protocols, including 0.3 mg, 0.45 mg, and 0.625 mg CE cores and subsequent pan loads leading to the 0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.45 mg/2.5 mg, and 0.625 mg/2.5 mg CE/MPA are presented in Table 6.1.4C.

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27 February 2001

Premarin/MPA / sNDA #20-527/S-017
Response to FDA

The following tables provide the dissolution profiles as follows:

Table No.	Strength	Formulation	Batch No.	Date of Manufacture
1	0.3/1.5 mg	Clinical	3THN	March 1994
2	0.3/1.5 mg	Clinical	1997B0093	July 1997
3	0.3/1.5 mg	Market	R982744	July 1998
4	0.3/1.5 mg	Market	R982745	July 1998
5	0.3/1.5 mg	Market	R982746	July 1998
6	0.45/1.5 mg	Clinical	3TEM	November 1993
7	0.45/1.5 mg	Clinical	1997B0089	July 1997
8	0.45/1.5 mg	Market	R982756	July 1998
9	0.45/1.5 mg	Market	R982757	July 1998
10	0.45/1.5 mg	Market	R982758	July 1998

The data represents the methods and specifications at the time of testing. For the Conjugated Estrogens results, the clinical formulation batches were tested with profiles at 1, 2, 4, 6, and 10 hours for information purposes while the market formulation batches were tested with profiles at 2, 5, and 8 hours for information purposes. The change to profiles at 2, 5, and 8 hours was to be consistent with the time points specified in USP 23, Supplement 8 for Conjugated Estrogens tablets which went into effect on May 15, 1998.

The data found in Tables 1-10 demonstrate that the clinical and market product batches are comparable in dissolution behavior. For drug release of Conjugated Estrogens, the method whereby profiles are generated over 8 or 10 hours, is discriminating and can detect minor differences in drug release for Conjugated Estrogens. The time points at which specifications have now been proposed are at 2, 5 and 8 hours.

For the dissolution of MPA all batches pass the specification of [redacted] (Q) at 45 minutes. All batches demonstrate rapid release.

Restricted

A brief description of the dissolution methods used to generate the data is provided below.

Method No.	Method Description
USP 23, Supplement 4	CE dissolution at — minutes USP Disintegration Apparatus 900 mL of simulated gastric fluid — analysis
3256-178	CE dissolution, method corresponds to current USP method for CE tablets USP Apparatus 2 (Paddles) 900 mL of water — analysis
2555-131	MPA dissolution USP Disintegration Apparatus 900 mL of 0.54% sodium lauryl sulfate — analysis

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 10, 1997

FROM: Angelica Dorantes, Ph.D., Team Leader
Division of Pharmaceutical Evaluation II/
Office of Clinical Pharmacology and Biopharmaceutics, HFD-870

TO: Vinod Shah, Ph.D.
Office of Pharmaceutical Sciences, HFD-350

ISSUE: Premarin: Dissolution test for medroxyprogesterone acetate.

SYNOPSIS

On March 20, 1997, Wyeth-Ayerst submitted a Supplement to NDA 20-527 for PREMPRO/PREMPHASE [conjugated estrogens (CE)/medroxyprogesterone acetate (MPA)] Tablets. Reference is made to the Wyeth-Ayerst Phase IV commitment to develop a new dissolution test for MPA which does not use the USP disintegration apparatus. This Supplement provides preliminary results on the development of a dissolution test for MPA. The following information has been provided (see Attachment I):

- Report GTR No. 27669 titled "Preliminary Report Using USP Dissolution Apparatus 3 for the Dissolution of MPA in Premarin/MPA", which describes the dissolution results using USP dissolution apparatus 3; 1 liter dissolution vessels.
- Method No. 4090-086 provides a description of the dissolution method.
- Method No. 2555-131 describes the current MPA dissolution method for Premarin/MPA.
- Report No. 24938 titled "Development and Rationale For Use of Medroxyprogesterone Acetate Dissolution Method 2555-131 For Premarin/MPA 0.625/2.5 mg and 0.625/5 mg Market Product Tablet", which evaluates the use of USP dissolution apparatus 1, 2, and USP disintegration apparatus without discs.

Wyeth-Ayerst states that once concurrence is received from the Agency for the use of the proposed method with USP apparatus 3 and 1 liter dissolution vessels, they will proceed to generate method validation data and test additional batches to set final specifications.

CONSULTATION REQUEST:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II would like to request that Dr. Vinod Shah evaluates the dissolution information submitted by Wyeth-Ayerst in support of the proposed dissolution method for MPA.

cc: NDA 20-527, HFD-580 (van der Vlugt, Moore), HFD-870 (Chen, Hunt, Dorantes), HFD-604 (Adams), HFD 350 (Shah), and CDR (B. Murphy for drug).

WYETH-AYERST LABORATORIES

ORIGINAL

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 341-2239
FAX: (610) 989-4596

Division of American Home Products Corporation

REGULATORY AFFAIRS

SUPPL NEW CORRESP

Noted 3/27/97 /S/

NDA No. 20-527
PREMPRO™ /PREMPHASE® Tablets

noted STL 2/5/97

March 20, 1997

Sent Consult to Dr. Shah. waiting for response. ANP 3/9/97

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

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

Noted NDR 7/12/95

PHASE IV COMMITMENT

Dear Dr. Rarick:

Reference is made to our New Drug Application No. 20-527 for PREMPRO/PREMPHASE (conjugated estrogens/medroxyprogesterone acetate) Tablets.

The purpose of this communication is to provide preliminary results on the development of a dissolution test for medroxyprogesterone acetate (MPA) and obtain FDA concurrence on this approach in meeting our Phase IV commitment to develop a new dissolution test for MPA which does not use the USP disintegration apparatus. The following information is provided:

Attachment I: GTR No. 27669 titled "Preliminary Report Using USP Dissolution Apparatus 3 for the Dissolution of MPA in Premarin/MPA," describes the results of this laboratory work. The methodology uses USP dissolution apparatus 3 using 1 liter dissolution vessels.

Attachment II: Method No. 4090-086 provides a description of the dissolution method.

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Draft Labeling
(not releasable