Pharmacokinetics of the First Combination 17β-Estradiol/Progesterone Capsule in Clinical Development for Hormone Therapy

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INTRODUCTION

- No FDA-approved combination product containing the natural hormones, 17β-estradiol and progesterone, exists.
- Combining 17β-estradiol and progesterone as a product with good bioavailability is difficult to achieve biochemically.
- Compounding pharmacies attempt to manufacture this combination, but such compounding should be viewed with caution.
  - Progesterone has poor bioavailability.[1]
  - The proper ratio of progesterone to estradiol in a combination formulation is difficult to achieve.
  - In two FDA surveys of compounding pharmacies, the amount of hormone contained in compounded products was not the amount claimed in approximately 34% of compounded products and 29% of hormone samples versus the <2% routinely found for commercially manufactured products.[2,3]
  - Pharmacokinetic studies of compounding pharmacy products are rarely performed.[4]
  - Progesterone levels in women taking compounded progesterone may not be sufficient for endometrial protection from estrogen stimulation.
- The investigational product (TX 12-001-HR) is the first oral combination 17B-estradiol/progesterone capsule (TherapeuticsMD, Inc., Boca Raton, FL) being studied for regulatory approval, and the first progesterone-containing combination without peanut oil. The progesterone and estradiol contained in the combination are chemically identical to the hormones of the human ovary.
- Under FDA guidance for 505(b)(2), relative bioavailability of any new product needs to be compared with the approved reference products, which for estradiol and progesterone are Estrace® and Prometrium®, respectively.

OBJECTIVES

- To determine the pharmacokinetics (PK) and oral bioavailability of a combination capsule of 17β-estradiol and progesterone (Test drug; TX12-001-HR)
- To compare Test drug PK and bioavailability with that of widely used individual formulations of the same: Estrace® (estradiol USP tablets 2 mg; Teva Pharmaceuticals, Sellersville, PA) and Prometrium® (progesterone softgel capsule 200 mg; Catalent Pharma Solutions, St. Petersburg, FL; Reference products) given together in healthy postmenopausal women under fed conditions.

SUBJECTS AND STUDY DESIGN

Subjects

- Key inclusion criteria: Healthy postmenopausal women aged 40 to 65 years with a BMI 18.50 to 29.99 kg/m2 who were nonsmokers or ex-smokers (no smoking in the last 3 months).
- Key exclusion criteria: Consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Study design

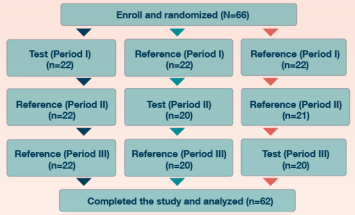
- Open-label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial-replicate, reference-scaled, oral, relative bioavailability study.
- Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of Test drug (T) and Reference products (R): TRR, RTR, or RRT.
- 24 blood samples were collected at multiple intervals from -1 h to 48 h relative to dosing.

RESULTS

Subject disposition and baseline characteristics

- 66 subjects were randomized and 62 (94.0%) completed the study (Figure 1).
- Subjects had a mean age of 49.5 ± 5.6 years (range 40 to 64) and a mean BMI of 24.8 ± 3.1 kg/m2 (range 18.7–29.9).

Figure 1. Disposition of the subjects



Relative bioavailability results

- All AUC and Cmax parameters met the bioequivalence criteria for all analytes, except Cmax for total estrone (Table). The extent of estradiol and progesterone absorption for the Test capsule appeared to be similar to that for the Estrace and Prometrium tablets, respectively.
- The rate of estradiol absorption (Tmax) for the Test capsule appeared to be slightly faster than that for Estrace.
- Semilogarithmic plots of AUC over time for each analyte are presented in Figures 2-3.

Table. Scaled Average Bioequivalence Analyses for Each Analyte

Analyte/Parameter	Test-to-Ref Ratio	CV%	95% Upper Confidence Bound	Meets BE Criteria*
Progesterone				
$AUC_{(0-t)}$	1.05	122.2	–0.5422	Yes
$AUC_{(0-inf)}$	0.94	116.4	–0.4941	Yes
C_{max}	1.16	173.7	–0.7850	Yes
Unconjugated estradiol				
$AUC_{(0-t)}$	0.93	42.6	–0.0888	Yes
$AUC_{(0-inf)}$	0.83	47.4	–0.0625	Yes
C_{max}	0.88	35.4	–0.0399	Yes
Unconjugated estrone				
$AUC_{(0-t)}$	0.89	18.0	0.848–0.938	Yes
$AUC_{(0-inf)}$	0.88	26.3	0.834–0.933	Yes
C_{max}	0.93	23.3	0.873–0.901	Yes
Total estrone				
$AUC_{(0-t)}$	1.06	29.7	0.982–1.115	Yes
$AUC_{(0-inf)}$	1.06	29.7	0.985–1.114	Yes
C_{max}	1.75	35.9	0.3438	No

*Scaled Average Bioequivalence requires Test-to-Reference ratio between 0.800 and 1.250 and the 95% upper confidence bound on the linearized statistic is ≤0. Unscaled Average Bioequivalence requires that the 90% confidence interval on the Test-to-Reference ratio is entirely within 0.800 and 1.250.
BE = bioequivalence; CV% = coefficient of variance.

Figure 2.
Progesterone: semilogarithmic plot of mean plasma concentration over time (N=62)

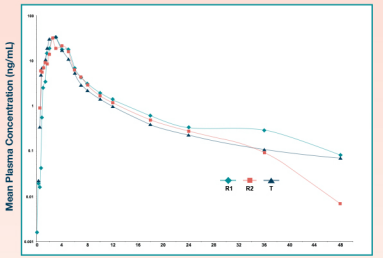
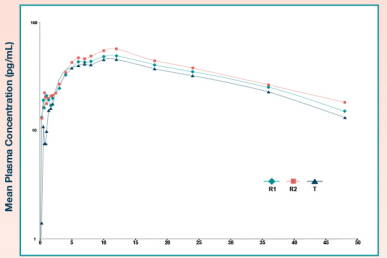


Figure 3.
Free estradiol: semilogarithmic plot of mean plasma concentration over time (N=62)



CONCLUSIONS

- The combination 17B-estradiol/progesterone product (TX 12-001-HR) demonstrated bioavailability of its constituents similar to that of their respective references of Estrace and Prometrium, when the reference products were given together under fed conditions.
- The relative bioavailability results would suggest the Test product combining natural progesterone and estradiol should have the same safety profile as that of the two reference products, Prometrium and Estrace, taken together.
- This new investigational therapy, if approved, would represent an exciting development in hormone therapy, as no approved hormone therapy to date has been able to
  1) Combine natural progesterone with 17β-estradiol as an oral formulation, and
  2) Offer the additional advantage of avoiding the use of peanut oil, a known allergen

References

1. McAuley JW, Kroboth FJ, Kroboth PD. Pharmacotherapy. 1996;16:453-457.
2. Food and Drug Administration. Report: Limited FDA survey of compounded drug products. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm. Accessed on July 19, 2013.
3. Food and Drug Administration. 2006 limited FDA survey of compounded drug products. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm. Accessed on July 19, 2013.
4. Bhavnani BR, Stanczyk FZ. J Clin Endocrinol Metab. 2012;97:756-759.

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