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APPLICATION NUMBER:

22-057

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-057	Submission Date(s): 08/21/2006
Brand Name	Endometrin® (Progesterone Effervescent Vaginal Tablets)
Generic Name	Progesterone
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III
OND division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Ferring Pharmaceuticals
Relevant IND(s)	68,097
Submission Type; Code	Standard
Formulation; Strength(s)	Vaginal Tablets; 100 mg
Indication	Progesterone supplementation in Assisted Reproductive Technology (ART)

An optional inter-divisional CPB briefing for NDA 22057 was held on April 25, 2007 (9 – 10 AM) in WO21 Room 4560; Attendees included Drs. Sandhya Apparaju, Myong Jin Kim, Dennis Bashaw, Hae Young Ahn, Donny Tran, Sandra Suarez, Jane Bai, Shashi Amur, Audrey Gassman, John Kim and Shiew Mei Huang.

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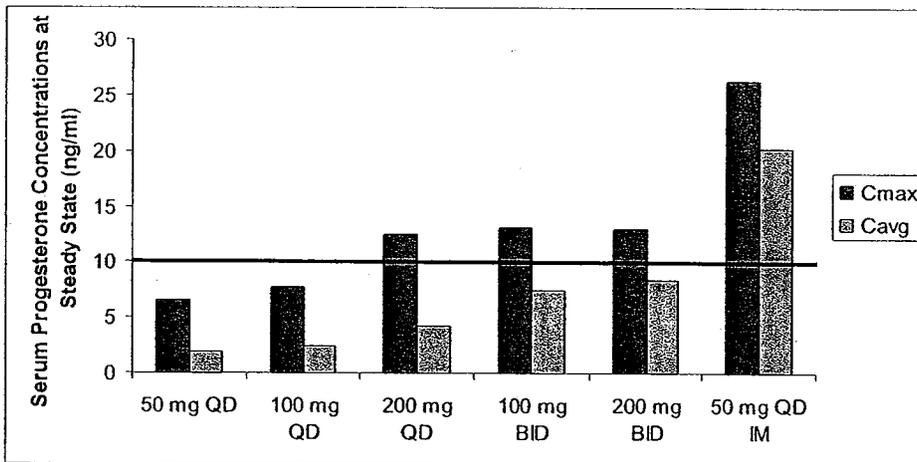


Figure 1: Serum progesterone concentrations (ng/ml) following various dose regimens employed in PK/PD study 2004-01. The hypothetical line at 10 ng/ml, represents acceptable “target” progesterone concentrations.

- Assessment of endometrial secretory transformation, as determined by biopsy was the primary basis for pharmacodynamic evaluation in this PK/PD study (2004-01).
- Majority of subjects (~60 %) in the two BID regimens had an endometrial biopsy demonstrating mid to late secretory stage (Figure 2). Subjects in the 50 mg and 100 mg QD regimens had an endometrial biopsy demonstrating non-secretory pattern with breakdown bleeding, inactive, or proliferative endometrial pattern.

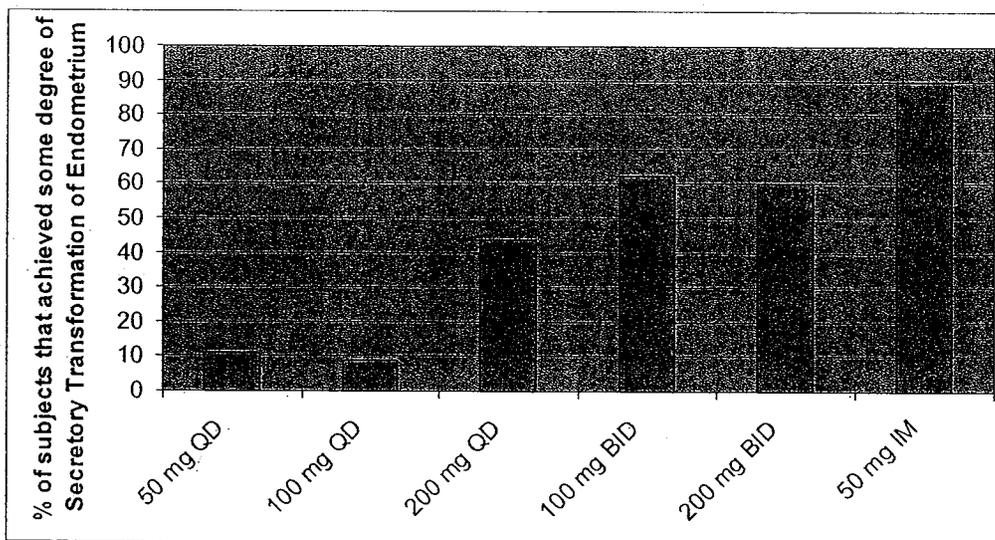


Figure 2: Pharmacodynamic end point (% achieving desired secretory transformation of the endometrium) across various dose regimens in study 2004-01

- Therefore, PK and PD results of this phase I PK/PD study support the use of doses at or above 100 mg BID in the phase 3 clinical trial in ART patients.

- Single-dose and multiple-dose PK of progesterone from Endometrin® vaginal tablets were assessed in Study 2004-01 and 2005-08. While both studies enrolled healthy pre-menopausal female volunteers, the study populations differed with respect to pre-treatment interventions (e.g. Gonadotropin-releasing hormone (GnRH) agonist use).
- Endometrin® vaginal tablets resulted in an increase in serum progesterone concentrations from baseline in pre-menopausal women of study 2004-01 who were pre-treated with GnRH agonist, Lupron. At a dose of 100 mg BID Endometrin (one of the two proposed regimens), the steady-state C_{max} was 13.2 ± 8.3 ng/ml, while the mean C_{avg} (7.47 ng/ml) was below the target concentration of 10 ng/ml.
- Tissue (uterine) progesterone concentrations were in general higher with Endometrin® vaginal tablets compared to intramuscular (IM) progesterone (reference). However, higher tissue levels did not result a greater percentage of patients to achieve the desired secretory transformation of endometrium (62.5 % with Endometrium® vs. 90 % with IM progesterone).
- In study 2005-08, the C_{avg} following multiple daily dosing of 100 mg BID, 100 mg TID and Crinone gel 90 mg QD were 17.68 ± 5.66 , 23.8 ± 5.8 , and 13.92 ± 6.26 ng/ml, respectively. In this study, both 100 mg BID and TID regimens of Endometrin® resulted in steady state C_{max} , C_{avg} and C_{min} concentrations that were at or above the desired 10 ng/ml target concentration, with the TID regimen demonstrating higher concentrations of the two regimens.
- Compared to the results of the earlier PK/PD study 2004-01, the single dose and steady-state serum progesterone exposures for the 100 mg BID regimen were higher in this study; the steady-state average serum progesterone concentrations (C_{avg}) were 7.4 ng/ml vs. 13.26 ng/ml in 2004-01 vs. 2005-08. While this could partly be due to inter-study variability, contribution from endogenous progesterone production in study 2005-08 due to the absence of Lupron pre-treatment could not be ruled out.
- Progesterone concentrations resulting from Endometrin® vaginal tablets in the PK subgroup of the large clinical trial 2004-02 were masked by markedly higher endogenous progesterone levels stimulated by ART in these patients. However, by the 4h time point on the day 16 (14th day of drug treatment), concentrations in women who did not achieve pregnancy (and thus would start menstruation) reached on average 7.95, 11.2 and 5.76 ng/ml, for Endometrin 100 mg BID, Endometrin 100 mg TID and Crinone 8 % gel QD, respectively. These concentrations are likely to have resulted from the drug source alone and results are consistent to that observed in earlier studies.
- There was no significant correlation between covariates such as age, or body weight (BW) and progesterone PK or between progesterone PK and the pregnancy outcome, within the PK subgroup of the phase 3 clinical trial.
- Age (< 35 years or 35-42 years) and ovarian reserve (FSH < 10 IU/ml or 10-15 IU/ml) appeared to have an influence on the pregnancy outcome in this trial. In the proposed package insert (PI), the sponsor recommends use of the

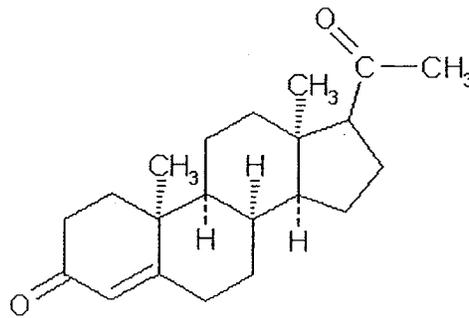
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2 QBR

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

- Endometrin® is an effervescent vaginal tablet containing 100 mg of progesterone (*pregn-4-ene-3,20-dione*, molecular weight 314.47) in each tablet.



C₂₁H₃₀O₂, M.W. 314.46

Figure 3: Structure of Progesterone

- Progesterone is a white or creamy white, odorless, crystalline powder. It is stable in air; practically insoluble in water; soluble in alcohol, acetone, dioxane and concentrated sulfuric acid; and sparingly soluble in vegetable oils. Progesterone exists as two crystalline forms (α - and β -) of equal physiologic activities, which are readily interconverted.
- The product uses an _____ of adipic acid and sodium bicarbonate. A list of all components of the dosage form and their functions is shown:

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Table 1: Endometrin® commercial formulation

Ingredient	Function
Progesterone, USP (Micronized)	Active pharmaceutical Ingredient
Colloidal Silicone Dioxide, NF _____	/
Lactose Monohydrate, NF _____	
Pregelatinized Starch, NF _____	
Polyvinylpyrrolidone, USP _____	
Adipic Acid, FCC	
Sodium Bicarbonate, USP	
Sodium Lauryl Sulfate, NF	
Magnesium Stearate, NF	

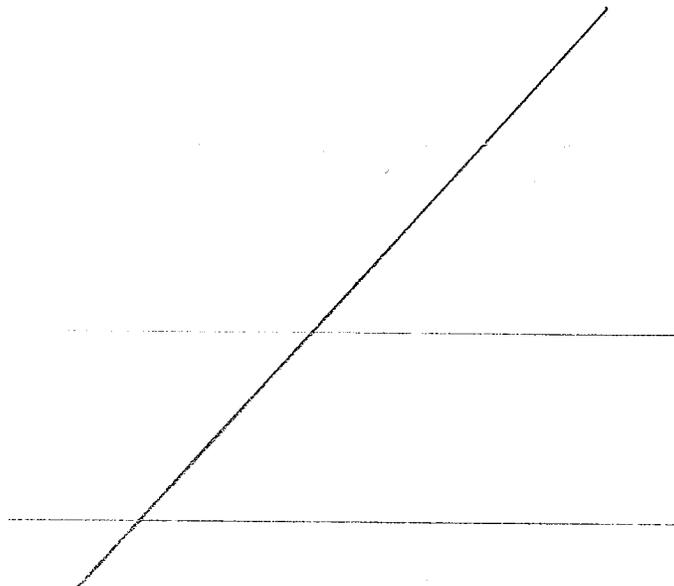
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- The tablets are packaged in aluminum/aluminum peel blisters. A commercially available insertion device is provided in the product package to facilitate the insertion of the tablet into the vagina.

2.1.2 What are the proposed mechanism of action and therapeutic indication?

- Therapeutic Indication: Endometrin® is indicated for progesterone supplementation in women undergoing ART.
- Mechanism of action and rationale for treatment: Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. It plays an important role in preparing the uterine lining for embryo implantation.
- The ovarian progesterone is responsible for maintaining the endometrium throughout the luteal phase of the menstrual cycle and, if pregnancy ensues, through the bulk of the first trimester until the placenta is able to assume responsibility for progesterone production just prior to the second trimester of pregnancy.
- In vitro fertilization and other ART treatments often involve suppression of normal ovarian function and, thus, result in the need for exogenous luteal phase support. Progesterone supplementation during the luteal phase of IVF cycles has become standard procedure, with the aim of supporting a corpus luteum that may have been compromised during ovulation induction and oocyte retrieval.
- Exogenous progesterone sources, which can maintain systemic progesterone levels of approximately 10 ng/ml are considered necessary to ensure successful establishment and maintenance of pregnancy in ART.

The Menstrual Cycle



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Figure 4: The menstrual cycle (source: <http://sprojects.mmi.mcgill.ca/menstrualcycle/home.html>); © 2000 Molson Medical Informatics Project

2.1.3 What are the proposed dosages and route of administration?

- Endometrin® tablets are intended to be administered vaginally, at a dose of 100 mg two or three times daily in women who require progesterone supplementation as part of ART.

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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

- Three clinical pharmacology studies have been submitted in this NDA. The first two are Phase I studies conducted in healthy pre-menopausal females. The third study is a Phase III clinical trial conducted in patients undergoing ART.
- Study 2004-01: A randomized, open-label, pharmacokinetic, pharmacodynamic and tolerability study of three dosage strengths (50 mg, 100 mg and 200 mg) and two administration regimens (QD and BID) of vaginal micronized progesterone tablet (Endometrin®) in healthy pre-menopausal female subjects.
- Study 2005-08: A randomized, open-label, single and multiple-dose pharmacokinetic study of vaginal micronized progesterone tablet (Endometrin® 100 mg BID or TID) compared to Crinone 8% vaginal gel (90 mg QD) in healthy pre-menopausal female subjects.
- Study 2004-02: A multi-center, randomized, open-label, parallel group study of vaginal micronized progesterone tablet (Endometrin® 100 mg BID or TID) compared to Crinone 8% vaginal gel (90 mg QD) in female patients undergoing in-vitro fertilization (IVF). A sub-group of this study contributed to PK data.

2.2.2 What is the basis for selecting the response endpoints (i.e. clinical) or biomarkers (PD) and how are they measured in clinical pharmacology and clinical studies?

- Pharmacodynamic (PD) endpoints of interest measured in phase I study 2004-01 included: secretory transformation of the endometrium (assessed by biopsy), tissue levels of progesterone (assessed using endometrial biopsy followed by RIA), intensity and percent of endometrial progesterone and estrogen receptor content (assessed by immunohistochemistry), and endometrial thickness (measured by transvaginal ultrasound).
- Coupled with acceptable serum levels of progesterone, presence of a secretory endometrium is generally considered to be essential for successful establishment and maintenance of pregnancy. Dose-response information obtained from

measurement of this PD endpoint in study 2004-01 was utilized to justify dose selection for the larger clinical trial of Endometrin® in women undergoing IVF.

- In the Phase III pivotal clinical trial, the primary endpoint was the rate of ongoing pregnancies, defined as identification of fetal heart movements at approximately 6 weeks of gestation.

2.2.3 Does this drug prolong the QT or QTc interval?

- No thorough QT studies have been conducted for Endometrin®, as the active ingredient is Progesterone, an endogenous steroidal hormone. Other formulations (i.m.) that result in higher systemic concentrations of progesterone than those seen with Endometrin® are currently approved.
- 12-Lead ECGs were obtained in the phase I PK/PD study in healthy premenopausal women. No statistically significant differences were observed among treatment groups in mean change from baseline to Day 10 (Final Visit) in QTc. Sporadic statistically significant differences were observed within treatment groups in mean change from baseline in QTc and ventricular rate. None of these differences were reportedly considered clinically meaningful and all mean values for ECG parameters remained within normal range.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response or concentration-response) for efficacy?

- Study 2004-01 was a PK/PD, dose-finding study in N = 57 healthy premenopausal women (18-40 years); women underwent hormonal down-regulation with a single injection of 3.75 mg Lupron depot prior to treatment. For eligibility to enter the Randomization/Treatment Phase, the serum progesterone concentration must have been ≤ 1 ng/mL.
- Treatments administered include micronized progesterone vaginal tablets (50 mg QD, 100 mg QD, 200 mg QD, 100 mg BID, and 200 mg BID) or Progesterone i.m. injection (50 mg/mL QD; reference), for a total of 10 days (n = 9-11 per group).

2.2.4.1.1 Relationship between dose and serum progesterone levels

- As shown in Figure 1, while the C_{max} values were above the physiological “target” for all dose regimens > 100 mg QD, none of the Endometrin® regimens evaluated in this study resulted in steady-state C_{avg} values above 10 ng/ml. The 100 mg and 200 mg BID dose levels demonstrated steady state C_{avg} values that approached the target exposure (7.47 and 8.31 ng/ml, respectively).
- The reference intramuscular progesterone (50 mg QD) resulted in pre-dose, C_{max} and C_{avg} concentrations that were > 10 ng/ml.

2.2.4.1.2 Relationship between progesterone dose/exposure and pharmacodynamic measures

2.2.4.1.2.1 Secretory transformation of the endometrium

- Assessment of secretory transformation, as determined by endometrial biopsy was the primary basis for PD assessment.
- The majority of subjects in the two BID regimens (~ 62 %) and in the reference IM group (90%) had an endometrial biopsy demonstrating mid to late secretory or secretory (not otherwise specified) status (Figure 2).
- The majority of subjects in the 50 mg and 100 mg QD regimens had an endometrial biopsy demonstrating non-secretory pattern with breakdown bleeding, inactive, or proliferative endometrial pattern. No consistent pattern was seen in endometrial biopsy results for subjects in the 200 mg QD group.

Table 2: Endometrial biopsy results to assess the primary PD endpoint (achieving a secretory transformation status of the endometrium) in study 2004-01

Endometrium Category	Endometrin					Progesterone IM (N=10)
	50 mg QD (N=9)	100 mg QD (N=11)	200 mg QD (N=9)	100 mg BID (N=8)	200 mg BID (N=10)	
Mid to late secretory (postovulatory Day 6-13)	1 (11%)	0 (0%)	1 (11%)	3 (38%)	5 (50%)	8 (80%)
Secretory, not otherwise specified	0 (0%)	1 (9%)	2 (22%)	2 (25%)	1 (10%)	1 (10%)
Weak secretory effect	0 (0%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)
Non-secretory pattern with breakdown bleeding	6 (67%)	5 (45%)	3 (33%)	1 (13%)	2 (20%)	1 (10%)
Inactive	0 (0%)	2 (18%)	0 (0%)	1 (13%)	1 (10%)	0 (0%)
Weakly proliferative	0 (0%)	1 (9%)	1 (11%)	0 (0%)	1 (10%)	0 (0%)
Active proliferative	2 (22%)	2 (18%)	1 (11%)	1 (13%)	0 (0%)	0 (0%)

Cross-reference: Table 14.3.4.5

- Reviewer conclusions: The PK (serum progesterone) and PD (secretory status) from 2004-01 support the use of Endometrin® BID dose regimens at doses ≥ 100 mg in the Phase 3 trial.

2.2.4.1.2.2 Tissue Progesterone Concentrations

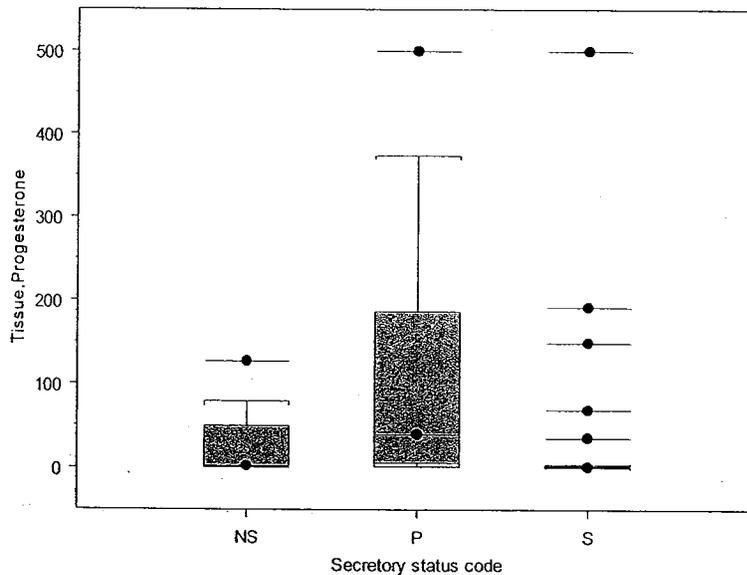
- The relationship between tissue progesterone levels and pregnancy outcome is not fully understood; Sponsor theorized that vaginal progesterone formulations result in a higher drug levels in uterine tissue and therefore there is a less reliance of systemic progesterone concentrations for efficacy. Tissue concentrations of progesterone were indeed higher in the Endometrin® vaginal tablet groups compared to IM progesterone. There was no consistent pattern of dose-related

increase in tissue concentrations within the various doses and regimens of Endometrin® vaginal tablets.

- Higher tissue progesterone concentrations however, did not result in a greater % of patients achieving desired secretory transformation of endometrium as shown in Table 3 below:

Table 3: Mean tissue progesterone concentrations and PD endpoint across various dose regimens in study 2004-01:

Treatment	50 mg QD	100 mg QD	100 mg BID	200 mg QD	200 mg BID	Reference IM 50 mg/ml QD
Tissue levels (ng/g)	48.87 ± 65.59	40.4 ± 66.59	7.14 ± 12.36	143.5 ± 205.5	102.27 ± 171.6	0.71 ± 0.26
% with Secretory endometrium	11 %	9 %	62.5 %	44.0 %	60 %	90 %



(NS: Non-secretory; P: Proliferative; S: Secretory)

Figure 5: Tissue progesterone concentrations grouped as per Secretory status of the endometrium.

2.2.4.1.2.3 Endometrial thickness

- According to the medical officer Dr. Audrey Gassman, Endometrial thickness as measured by transvaginal ultrasound may not be a reliable PD marker of efficacy, due to inter- and intra- individual error associated in measuring this parameter.
- Ideally endometrial thickness should increase in luteal phase. In this study, the Endometrin® groups showed a decrease in the endometrial thickness by day 10 of

treatment, while an increase was observed with the reference (IM) treatment. These results were therefore inconclusive.

Table 4: Change in Endometrial thickness from the end of priming phase to day 10 (final visit) by transvaginal ultrasound.

Endometrial Thickness (mm)	Endometrin					Progesterone IM (N=10)
	50 mg QD (N=9)	100 mg QD (N=11)	200 mg QD (N=9)	100 mg BID (N=9)	200 mg BID (N=10)	
End of Priming Mean (SD)	8.79 (3.107)	9.22 (3.221)	9.30 (1.806)	10.89 (3.242)	11.22 (3.454)	10.31 (3.230)
Median	9.00	7.90	9.10	10.00	11.25	9.55
Min, max						
p-value ^a = 0.429						
Day 10/Final Mean (SD)	7.52 (3.681)	6.19 (2.030)	7.17 (2.270)	(N=8) 8.36 (3.551)	10.20 (4.115)	12.36 (4.175)
Median	6.30	6.10	7.00	7.55	9.75	12.15
Min, max						
Change to Final Mean (SD)	-1.27 (3.235)	-3.03 (3.080)	-2.13 (2.210)	(N=8) -1.75 (3.049)	-1.02 (1.430)	2.05 (2.638)
Median	-1.70	-3.60	-3.10	-2.30	-0.80	1.50
Min, max						
p-value ^a = 0.002*						
p-value ^b	p=0.274	p=0.009*	p=0.020*	p=0.148	p=0.050*	p=0.036*

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* Statistically significant difference (p<0.05).

a Across-group p-value from a one-way ANOVA.

b Within-group p-value from a paired t-test.

Cross-reference: Table 14.3.5.6

2.2.4.1.2.4 Endometrial Progesterone receptor content

- Immunohistochemistry results in general served to confirm the biopsy results. Results showed that in endometrial biopsies that demonstrated mid to late secretory status, only a smaller % of cells (0 to 16%) were stained and the stain was at a lower intensity (score 0-19), compared to the cell staining observed in non-secretory/ proliferative biopsies. This finding supports the theory that progesterone receptors are down-regulated in the secretory phase.

Table 5: Immunohistochemistry results grouped by endometrial status (PD)

Secretory transformation: Yes			Secretory transformation: No		
	PR.Percent	PR.Intensity		PR.Percent	PR.Intensity
Min:			Min:		
Mean:	3.187500	9.75000000	Mean:	51.31818	60.72727
Median:	0.000000	1.50000000	Median:		
Max:			Max:	100.00000	120.00000
Std Dev.:	9.005323	18.44089658	Std Dev.:	44.74732	35.76934
LCL Mean:	-1.611098	-0.07646016	LCL Mean:	31.47833	44.86803
UCL Mean:	7.986098	19.57646016	UCL Mean:	71.15803	76.58651

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- Safety:** One or more AEs were reported by 1 (11%) subject in the 50 mg QD group, 5 (45%) subjects in the 100 mg QD group, 4 (44%) subjects in the 200 mg

QD group, 5 (56%) subjects in the 100 mg BID group, 4 (40%) subjects in the 200 mg BID group, and 6 (60%) subjects in the Progesterone IM group. Across all Endometrin® treatment groups, dysmenorrhea, headache, nausea were observed.

Reviewer conclusions:

- *Dose-response was established in this study in terms of the PD endpoints of interest, namely “secretory transformation of endometrium” (exploratory) and “serum progesterone levels”.*
- *Doses at or below 100 mg QD regimen were inadequate in resulting sufficient luteal phase transformation of the endometrium and also in maintaining adequate serum progesterone levels.*
- *The BID regimens of Endometrin® vaginal tablets, at doses \geq 100 mg, resulted in progesterone Cavg of approximately 8 ng/ml and achieved secretory transformation of the endometrium in ~62.5 % of the subjects, thus supporting their use in the phase 3 clinical trial.*

2.2.5 Pharmacokinetics

2.2.5.1 What are the single dose and multiple dose PK parameters?

2.2.5.1.1 Study 2004-01

- Single dose and multiple dose (day 10) pharmacokinetics of serum progesterone from Endometrin® vaginal tablets were evaluated following various doses and dose regimens.
- This study enrolled pre-menopausal healthy women (n = 9-11 per group; 18-40 years), who were pre-treated with a GnRH agonist (3.75 mg Lupron depot) and therefore had progesterone levels at entry of < 1 ng/ml.
- Treatments included Endometrin® progesterone vaginal tablets (50 mg QD, 100 mg QD, 200 mg QD, 100 mg BID, and 200 mg BID) and Progesterone i.m. injection (50 mg/mL QD), for a total of 10 days.
- A blood sample for PK analysis was obtained before the first dose of study medication was administered. Additional blood samples were collected for PK analysis at 0.5, 1, 2, 4, 6, 8, 12 h, and at 24, 36, 48, 72, 96 and 168 hours post-first dose.
- A blood sample for PK analysis was obtained before the last dose of study medication was administered. *On Day 10, only the morning dose was administered to subjects in BID dosing groups.* At the Final Visit, blood samples were collected for PK analysis at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose;

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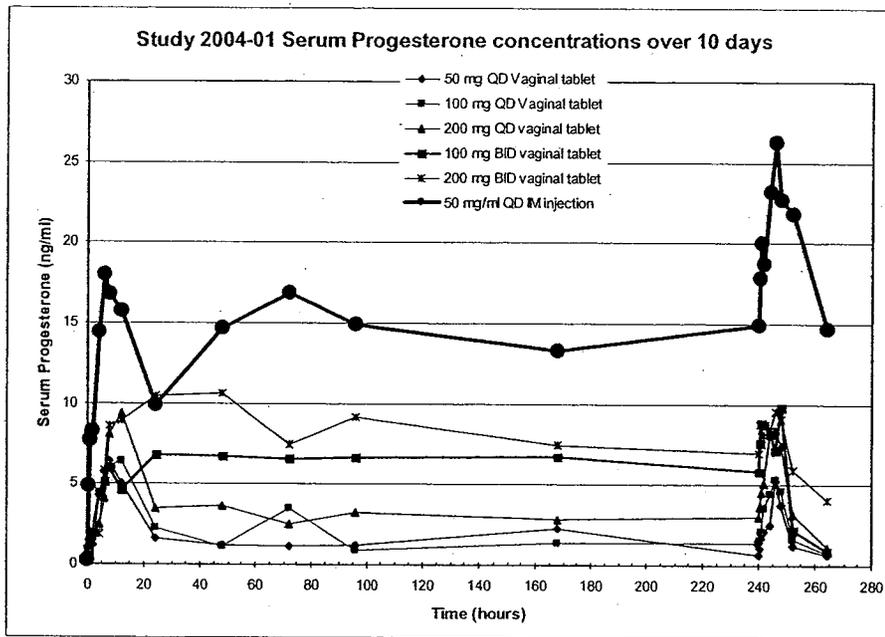
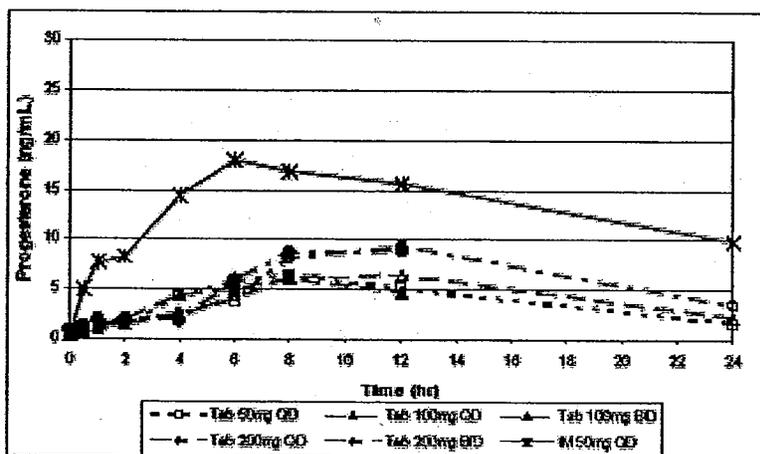


Figure 6: Serum progesterone concentrations over 10 days during PK/PD study 2004-01 (only trough levels are shown for days 2-8)

Single dose PK:

- Baseline values of serum progesterone were low (~ 0.25 ng/ml) due to pre-treatment with GnRH agonist drug, Lupron. Serum progesterone concentrations increased from baseline following single doses of Endometrin® vaginal tablets. Concentrations were higher than baseline at the very first sample obtained 0.5 h post-dose in all treatment groups.
- Progesterone from the vaginal tablets peaked at ~ 8-12 h post-dose.



Cross-reference: Appendix 16.1.13, PK Report, Figure 1A

Figure 7: Serum Progesterone levels following the first dose on day 1 (profiles for the two BID regimens include concentrations resulting from both doses administered during the 24 h period)

- Compared to IM progesterone, the vaginal tablets resulted in lower serum progesterone concentrations. Single dose Cmax values from the vaginal tablets ranged from 8-12 ng/ml, compared to a Cmax of ~ 20 ng/ml from the IM progesterone.
- Single dose PK of Endometrin® vaginal tablets suggest that with increase in the dose from 100 mg to 200 mg, there was a less than dose-proportional increase in Cmax and AUC, for both the QD and BID regimens.

Table 6: Serum progesterone pharmacokinetics (mean ± SD) on day 1 (single dose) and on day 10 (steady-state) of study 2004-01:

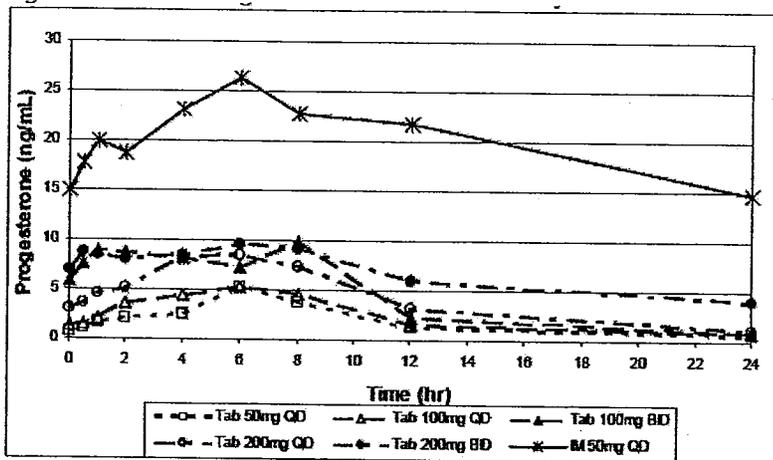
	Endometrin					Progesterone
	50 mg QD	100 mg QD	200 mg QD	100 mg BID	200 mg BID	IM
Day 1 (Visit 5) Pharmacokinetic Parameters						
Cbase (ng/mL)	0.278±0.126	0.286±0.172	0.296±0.125	0.283±0.180	0.878±1.779	0.262±0.117
Cmax (ng/mL)	8.06±2.43	8.29±2.87	11.5±3.9	8.06±3.57	11.3±4.0	20.0±5.3
Baseline Corrected Cmax (ng/mL)	7.78±2.50	8.01±3.02	11.2±3.9	7.78±3.54	10.4±4.7	19.7±5.3
Tmax (hr)	7.56±2.96	10.7±4.9	12.0±4.9	7.33±3.16	10.2±2.4	8.20±2.74
AUC(0-t) (ng·hr/mL)	92.3±20.7	98.8±33.8	138±35	50.5±20.7	64.1±27.9	320±67
Baseline Corrected AUC(0-t) (ng·hr/mL)	85.6±20.2	91.9±36.9	131±34	47.1±20.3	60.4±30.4	313±67

Steady-state PK	50 mg QD	100 mg QD	200 mg QD	100 mg BID	200 mg BID	50 mg QD IM
Tmax (h)	5.44 ± 2.47	5.45 ± 2.21	4.73 ± 3.08	3.31 ± 3.43	5.88 ± 4.13	7.15 ± 2.23
Css,max (ng/ml)	6.6 ± 2.4	7.7 ± 1.9	12.5 ± 2.7	13.1 ± 8.3	12.9 ± 4.5	30.3 ± 7.6
Cavg (ng/ml)	4.9 ± 0.5	2.45 ± 0.8	4.25 ± 1.0	7.47 ± 3.83	8.5 ± 2.7	20.1 ± 3.0
AUC0-t ng.h/ml	45.8 ± 11.9	58.9 ± 19.4	102 ± 25	89.6 ± 45.9	99.6 ± 44.8	479 ± 71

Note: AUC0-t represents area under the curve over 12 h or 24 h, depending on whether drug was administered BID or QD. Baseline correction was made by subtracting the relevant pretreatment progesterone concentration from the Cmax, or the product of the baseline concentration and the dosing interval, from the AUC over the dosing interval; Cl/F, the apparent clearance, was calculated as the dose administered, divided by the baseline corrected AUC over the dosing interval following the last dose; Dose-Normalized AUC0-t was obtained by dividing the baseline-corrected AUC0-t by total dose (in mg) administered on day 10; only the morning dose of Endometrin® was administered on this final day, even for the two BID regimens.

Multiple dose PK:

Appears This Way
On Original



Cross-reference: Appendix 16.1.13, PK Report: Figure 2

Figure 8: Serum progesterone levels following the last dose on day 10

- Trough levels obtained on days 2, 3, 4, 6, 8 and 10 days post-dose suggest that steady-state levels were achieved by the end of first day of dosing.
- Drug accumulation (up to 2.0-fold) with multiple daily dosing for 10 days was observed only for the two BID regimens (100 mg BID and 200 mg BID) of Endometrin® vaginal tablets. The QD regimens had steady-state exposure that was lower than that following a single dose on day 1. The reason for this discrepancy is not clear.
- The average steady-state serum progesterone concentrations (C_{avg}) increased with dose but in a less than dose-proportional manner, across the QD and BID regimens. The 3 QD tablet treatment groups (50, 100 and 200 mg tablets) had C_{avg} ratios of 1:1.28:2.23 compared to their dosing ratios of 1:2:4. The BID doses had mean C_{avg} ratios of 1:1.11, while the dosing ratios were 1:2.
- The BID dosing frequency in general, resulted in higher serum levels compared to the QD regimen. At Endometrin® doses of 100 mg and 200 mg, the BID regimens provided average serum levels of 7.47 and 8.31 ng/ml, respectively, compared to 2.45 and 4.25 ng/ml following once daily (QD) regimens. C_{avg} for the 50 mg QD dose was 1.91 ng/ml. Similarly, the trough concentrations were also higher for the BID regimens compared to when the dose was given once daily.
- The IM progesterone (90 mg QD) regimen demonstrated a higher steady state progesterone exposure compared to Endometrin® vaginal tablets. The steady-state C_{avg} of progesterone following 10 days of daily dosing with intramuscular progesterone was 20.2 ng/ml, well above the desired target concentrations of ~ 10 ng/ml.
- At the proposed dose of 100 mg BID, the relative bioavailability of Endometrin® tablets compared to IM progesterone was estimated to be ~ 8 % based on AUC_{0-τ}, and ~ 20 % based on C_{max}.
- *Reviewer conclusions: Results of study 2004-01 suggest that in premenopausal women pre-treated with GnRH agonist, Lupron, Endometrin®*

vaginal tablets resulted in an increase in serum progesterone concentrations from baseline. At the proposed 100 mg BID dose regimen (one of the two) evaluated in this study, the steady-state C_{max} was 13.2 ± 8.3 ng/ml, while the C_{avg} value of 7.47 ng/ml was below the target concentration of 10 ng/ml.

Presence of residual vaginal tablets:

- In this study, 8 women (1 in 50 mg QD, 2 each in 100 mg QD and 200 mg QD, and 3 in 200 mg BID) were reported to have residual vaginal tablets during vaginal exam on the last day. Vaginal exam was done approximately 5-6 hours post-morning dose on that day, and tablet findings were generally described by the sponsor as presence of a part or residual of tablet. The total count of such residual tablets found in each such subject was in general either similar or less than the total count of tablets that the patient would have received that morning, based on their randomized dose level.

Table 7: Steady-state progesterone PK parameters of interest in subjects with residual vaginal tablets; the group mean and range for the PK parameter are shown in parentheses.

Subject #	Treatment	T _{max} (h)	C _{max} (ng/ml)	C _{avg} (ng/ml)	AUC _{tau} (ng.h/ml)	Tissue progesterone ng/g	Secretory Status Y/N; (% success in group)
2025	50 mg QD	6 (5.3; 6.5)	4.49 (6.59; 13.2)	1.36 (1.91; 2.31)	32.6 (45.8; 55.5)	62.19 (48.8; 191.59)	No (14.2%)
2005	100 mg QD	8 (5.45; 8)	6.68 (7.7; 13.2)	2.31 (2.45; 2.98)	55.5 (58.9; 71.56)	191.59 (40.4; 18.65)	Yes (12.5%)
2019	100 mg QD	8 (5.45; 8)	8.79 (7.7; 13.2)	2.98 (2.45; 2.29)	71.56 (58.9; 55.09)	18.65 (40.4; 500)	No (12.5%)
2033	200 mg QD	4 (4.7; 4)	7.49 (12.45; 15.33)	2.29 (4.25; 5.06)	55.09 (102; 102.95)	500 (143.5; 500)	No (57.1%)
2060	200 mg QD	4 (4.7; 4)	15.33 (12.45; 11.96)	5.06 (4.25; 8.57)	121.52 (102; 99.67)	500 (91.15; 140)	No (57.1%)
2008	200 mg BID	6 (5.8; 5.8)	11.96 (12.98; 13.87)	8.57 (8.3; 7.76)	102.95 (99.67; 93.17)	500 (91.15; 140)	Yes (62.5%)
2030	200 mg BID	12 (5.8; 5.8)	13.87 (12.98; 10.75)	7.76 (8.3; 6.54)	93.17 (99.67; 78.55)	140 (91.15; 39.9)	Yes (62.5%)
2046	200 mg BID	2 (5.8; 5.8)	10.75 (12.98; 13.87)	6.54 (8.3; 7.76)	78.55 (99.67; 102.95)	39.9 (91.15; 140)	No (62.5%)

b(4)

Reviewer conclusions: A comparison of PK and PD data from individuals with residual vaginal tablets, to those observed in other women from their dose groups did not identify any conclusive trends, with respect to serum or tissue levels or achievement of the secretory transformation of endometrium (PD).

2.2.5.1.2 Study 2005-08

- In this study, single dose and multiple dose PK for the two proposed dosing regimens of Endometrin® vaginal tablets (100 mg BID and 100 mg TID) were evaluated, and compared to that of an approved vaginal progesterone gel product (Crinone gel 90 mg QD).
- Study 2005-08 was a single center, randomized, open-label Pharmacokinetic study in N = 18 (6 per group) healthy pre-menopausal female volunteers;
- Unlike study 2004-01, subjects were not pre-treated with a GnRH agonist drug. All women were randomized between day 5 and 8 of their menstrual cycle and not before menstrual bleeding has completely ceased.
- Study involved a single dose phase (1 Day) and multiple dose phase (5 days), separated by a wash-out period of 7 days. No baseline correction was done.
- Subjects were randomized to one of the following treatments: 1) Endometrin® 100 mg BID, 2) Endometrin® 100 mg TID, and 3) Crinone 90 mg QD.
- Single dose and multiple dose PK were obtained after Day 1 dosing and after the final day of dosing (day 5) of the multiple dose phase, for 48 hours (0, 2, 4, 8, 12, 16, 24, 36, 48 h) post-dose; trough concentrations were obtained in between days for assessment of steady state.
- *All doses in a BID or TID regimens (2 or 3) were to be administered on day 5 (last day of multiple dosing), unlike the earlier study where only the morning dose of the BID regimen was to be administered on the final PK day. Therefore, 24-h steady-state sampling in study 2005-08 encompasses concentrations resulting from all doses administered during the 24-hour period on day 5.*

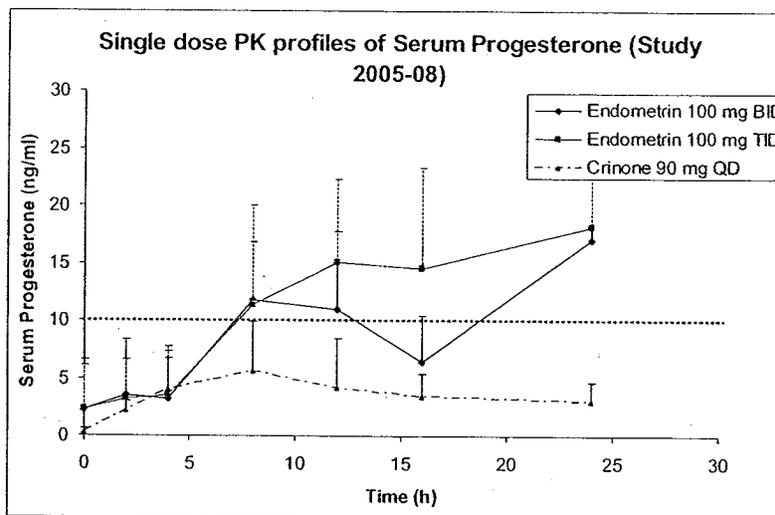


Figure 9: Single dose PK profiles of serum progesterone from study 2005-08

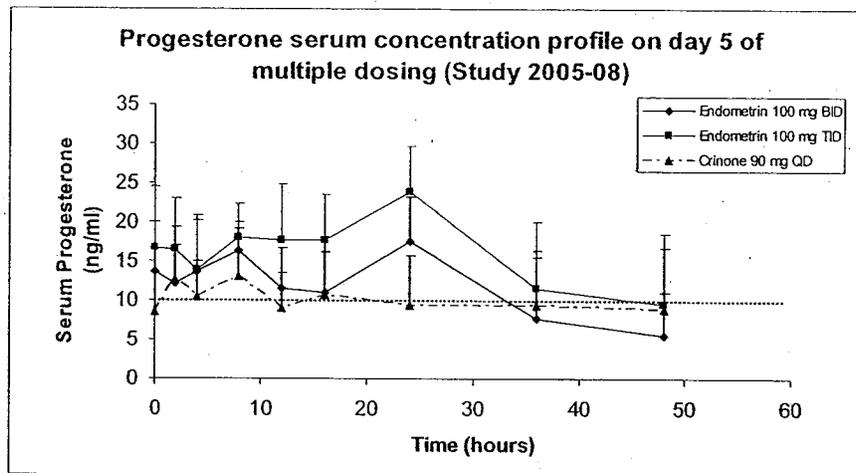


Figure 10: Progesterone serum concentrations on day 5 of multiple dosing phase in study 2005-08.

Table 8: Mean \pm SEM serum progesterone pharmacokinetics from study 2005-08

Pharmacokinetic Parameter (unit)	Endometrin 100 mg BID (N=6)	Endometrin 100 mg TID (N=6)	Crinone 90 mg QD (N=6)
	Mean \pm SEM	Mean \pm SEM	Mean \pm SEM
Single Day of Dosing			
C_{max} (ng/mL)	17.0 \pm 2.7	19.8 \pm 2.9	6.82 \pm 1.69
T_{max} (hr)	24.0 \pm 0.0	17.3 \pm 3.0	13.3 \pm 2.5
$AUC_{0-\tau}$ (ng·hr/mL)	88.4 \pm 21.1	41.7 \pm 15.5	80.9 \pm 17.0
AUC_{0-24} (ng·hr/mL)	217 \pm 46	284 \pm 58	80.9 \pm 17.0
Day 5 of Multiple Days of Dosing			
C_{max} (ng/mL)	18.5 \pm 2.3	24.1 \pm 2.3	14.3 \pm 2.3
T_{max} (hr)	18.0 \pm 3.8	18.0 \pm 3.8	12.3 \pm 5.2
C_{min} (ng/mL)	8.90 \pm 1.85	10.9 \pm 2.7	7.40 \pm 1.43
T_{min} (hr)	10.7 \pm 2.8	3.67 \pm 1.09	6.67 \pm 3.96
$AUC_{0-\tau}$ (ng·hr/mL)	167 \pm 24	127 \pm 14	264 \pm 46
AUC_{0-24} (ng·hr/mL)	327 \pm 52	436 \pm 43	264 \pm 46
CI/F (L/hr)	657 \pm 87	846 \pm 112	417 \pm 95
Fluctuation Index (ratio)	0.769 \pm 0.106	0.783 \pm 0.137	0.701 \pm 0.149
C_{min}/C_{max} (ratio)	0.464 \pm 0.045	0.425 \pm 0.084	0.504 \pm 0.060

Cross-reference: Appendix 16.1.13, PK Report: Table 2

- On the first day of dosing, AUC_{0-24h} was 217 ng.h/ml in the Endometrin® BID group, 284 ng.h/ml in the Endometrin® TID group, and 81 ng.h/ml in the Crinone group (the total vaginal dose (mg) of progesterone received on day 1 during these three regimens was 200 mg, 300 mg and 90 mg, respectively).
- The progesterone concentrations approximated steady-state concentration by the time the second dose was administered (12 hours after the first dose) in the BID

regimen and by the time of the second dose on Day 2 (32 hours after the start of dosing) for Endometrin TID. Steady-state serum progesterone concentrations for both Endometrin regimens exceeded the physiologically significant level of ~10 ng/mL for the entire day.

- The reviewer calculated steady state progesterone levels, following multiple daily doses of Endometrin® 100 mg BID, 100 mg TID and Crinone® 90 mg QD are shown:
 - C_{max} : 17.68 ± 5.66 , 23.84 ± 5.84 , and 13.9 ± 6.3
 - C_{avg} : 13.26 ± 5.87 , 20.78 ± 5.16 , and 10.58 ± 5.13 ng/ml and
 - C_{min} : 9.6 ± 6.1 , 17.7 ± 5.8 , 7.0 ± 3.8 ng/ml, *respectively*.
- Both the BID and TID regimens resulted in steady state C_{max} , C_{avg} and trough concentrations that were at or above the desired 10 ng/ml target concentration, with the TID regimen demonstrating higher concentrations of the two regimens.
- *Compared to the results of the earlier PK/PD study 2004-01*, the single dose and steady-state serum progesterone exposures (AUC_{0-12h}) for the 100 mg BID regimen were higher in this study; the steady-state average serum progesterone concentrations (C_{avg}) were 7.4 ng/ml vs. 13.26 ng/ml in 2004-01 vs. 2005-08.
- While this could partly be due to inter-study variability, another cause could be that the two study populations are different: in study 2005-08 absence of Lupron pre-treatment could have resulted in presence of endogenous progesterone levels.

Table 9: Cross-study comparison of steady state PK following Endometrin 100 mg BID

100 mg BID Endometrin®	Study 2004-01 (mean ± SD)	Study 2005-08 (mean ± SEM)
C_{avg} , MD	7.5 ± 3.8	13.3 ± 2.39
AUC_{tau} , MD	89.7 ± 45.7	167 ± 24
CL/F (L/h)	1432 ± 664	657 ± 87

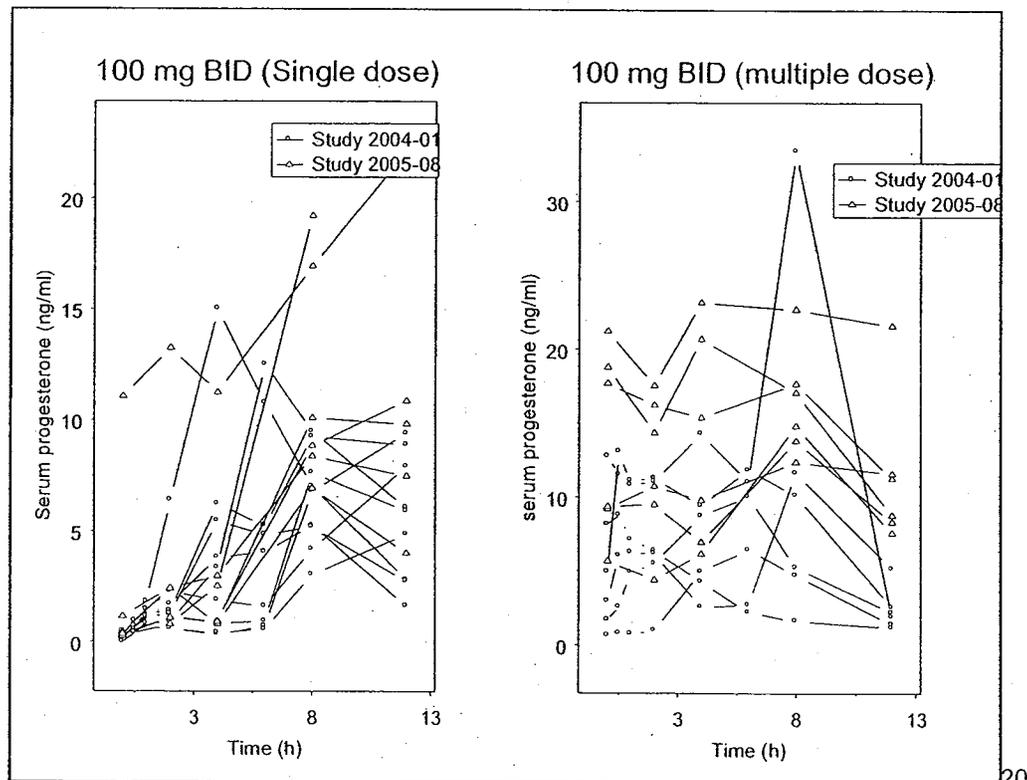


Figure 11: Cross-study comparisons of serum progesterone concentrations (ng/ml) in individuals of study 2004-01 and study 2005-08 dosed with Endometrin 100 mg BID.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

- Endometrin® is proposed for use in otherwise healthy, pre-menopausal females undergoing ART. Therefore, the intended “patient” population is not significantly different from healthy female volunteers. However, endogenous levels of hormones could differ between these two populations.
- In healthy, pre-menopausal woman not undergoing ART, there is a natural rise and fall of serum progesterone levels during the course of the menstrual cycle, with progesterone concentrations at peak after ovulation (Figure 4). Therefore, it is likely that in women not pre-treated with GnRH agonist such as Lupron (e.g. subjects of study 2005-08) observed PK following administration of Endometrin vaginal tablets may be confounded by endogenous levels of progesterone. This probably was responsible for at least part of the observed differences in serum levels at the 100 mg BID dose level in study 2005-08 compared to study 2004-01, in which healthy women volunteers first underwent endogenous hormone down-regulation with Lupron pre-treatment.
- ART patients may also experience significant changes in their endogenous hormone levels. Initially, administration of a GnRH agonist or antagonist (to prevent premature LH surge that allows greater number of oocytes to reach maturity) and the process of oocyte retrieval may cause a relative progesterone deficiency. Eventually patients may experience high progesterone levels due to ovarian stimulation by exogenous hCG injection (for up to a week or two post-retrieval), and later on if the outcome is successful, from pregnancy-related hCG.
- Therefore, while it is unknown whether progesterone supplementation is needed for all subjects, or what the timing of supplementation should be, it is assumed that supplementation needs to be started at hCG stimulation prior to embryo transfer. The rationale behind this is that progesterone supplementation should closely mimic a normal menstrual cycle with progesterone rising during ovulation (hCG stimulation).
- Due to these endogenous changes in hormones, in a typical patient population the true PK resulting from an exogenous drug source may be masked, as was observed in the phase 3 clinical trial 2004-02:

2.2.5.2.1 *Study 2004-02 (Phase 3)*

- In this phase 3 clinical trial, even though the baseline serum progesterone levels at entry were < 1 ng/ml (due to GnRH agonist pre-treatment), serum progesterone levels began to rise starting two days prior to the administration of exogenous progesterone, probably due to ovarian stimulation by the exogenous-hCG injection administered for final follicular maturation. Therefore, all women demonstrated markedly high serum progesterone levels

for up to 9 days post-retrieval. Concentrations remained markedly high at all time points as shown below, thereby masking the true concentrations resulting from exogenous drug sources alone (Endometrin BID, TID or Crinone QD).

Table 10: Day 7 progesterone pharmacokinetic parameters in patients who became pregnant in study 2004-02 (phase 3 clinical trial)

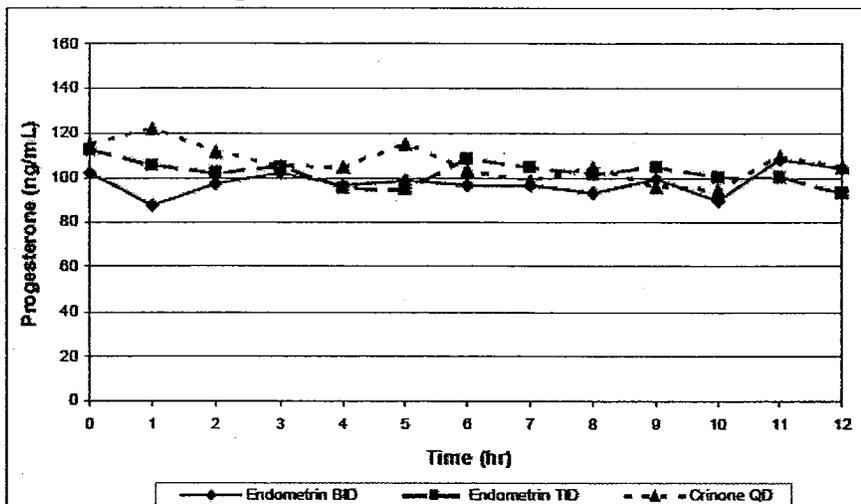
Day	Hour	Endometrin BID		Endometrin TID		Crinone QD	
		N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
C _{max}	ng/mL	3	112 ± 39	3	122 ± 36	5	131 ± 17
T _{max}	hr	3	5.00 ± 3.21	3	2.67 ± 2.19	5	4.20 ± 1.83
C _{min}	ng/mL	3	84.2 ± 29.6	3	83.9 ± 32.6	5	79.8 ± 15.2
T _{min}	hr	3	5.33 ± 2.60	3	10.00 ± 1.53	5	6.20 ± 2.13
AUC(0-4)	ng·hr/mL	3	1167 ± 402	3	820 ± 265	5	2594 ± 376
AUC(0-12)	ng·hr/mL	3	1167 ± 402	3	1220 ± 392	5	1275 ± 181
C _{avg}	ng/mL	3	97.3 ± 33.5	3	102 ± 33	5	106 ± 15
Fluctuation Index	ratio	3	0.277 ± 0.030	3	0.422 ± 0.100	5	0.524 ± 0.102
C _{min} /C _{max}	ratio	3	0.762 ± 0.024	3	0.658 ± 0.066	5	0.590 ± 0.065
Day 5/Day 2 C ₄ /C _{max}	ratio	3	15.7 ± 4.17	3	9.23 ± 1.37	5	9.40 ± 1.05

Table 11: Day 7 progesterone pharmacokinetic parameters in patients who did not become pregnant in study 2004-02 (phase 3 clinical trial)

Day	Hour	Endometrin BID		Endometrin TID		Crinone QD	
		N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
C _{max}	ng/mL	3	150 ± 68	4	113 ± 35	5	82.7 ± 11.3
T _{max}	hr	3	3.67 ± 2.73	4	4.00 ± 1.58	5	5.20 ± 1.93
C _{min}	ng/mL	3	99.0 ± 47.8	4	65.1 ± 21.1	5	54.5 ± 10.8
T _{min}	hr	3	7.67 ± 3.33	4	8.25 ± 1.03	5	6.80 ± 1.77
AUC(0-4)	ng·hr/mL	3	1472 ± 677	4	712 ± 225	4	1625 ± 298
AUC(0-12)	ng·hr/mL	3	1472 ± 677	4	1035 ± 303	4	828 ± 141
C _{avg}	ng/mL	3	123 ± 56	4	86.3 ± 25.2	4	69.0 ± 11.8
Fluctuation Index	ratio	3	0.457 ± 0.073	4	0.578 ± 0.077	4	0.468 ± 0.134
C _{min} /C _{max}	ratio	3	0.631 ± 0.051	4	0.557 ± 0.052	5	0.652 ± 0.084
Day 5/Day 2 C ₄ /C _{max}	ratio	3	9.76 ± 0.74	4	13.4 ± 1.7	5	9.62 ± 0.72

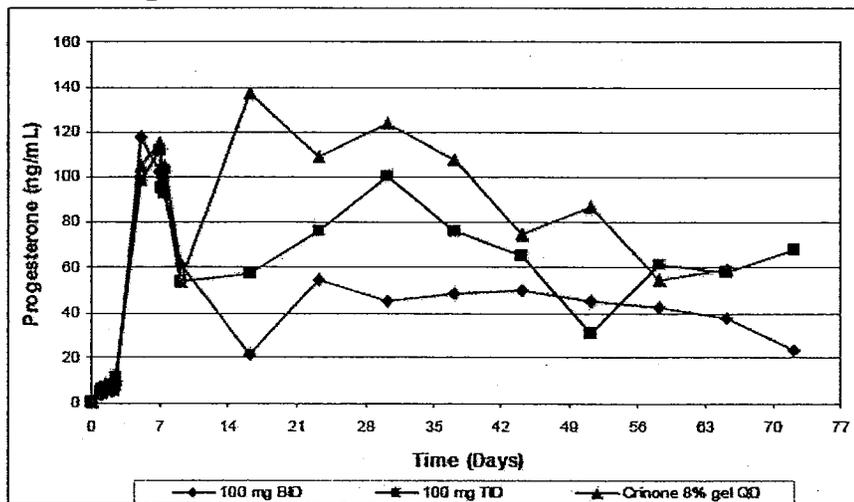
- In women who achieved pregnancy, serum concentrations declined gradually over 9- 72 days post-dose (based on single weekly samples at the 4 h time point) probably due to declining contribution from the initial hCG injection. However, concentrations were still markedly higher than what would result from exogenous progesterone source alone, probably as a result of increase in ovarian progesterone supply from pregnancy-hCG.

Figure 12: Mean day 7 serum progesterone concentrations in IVF patients who became pregnant in study 2004-02



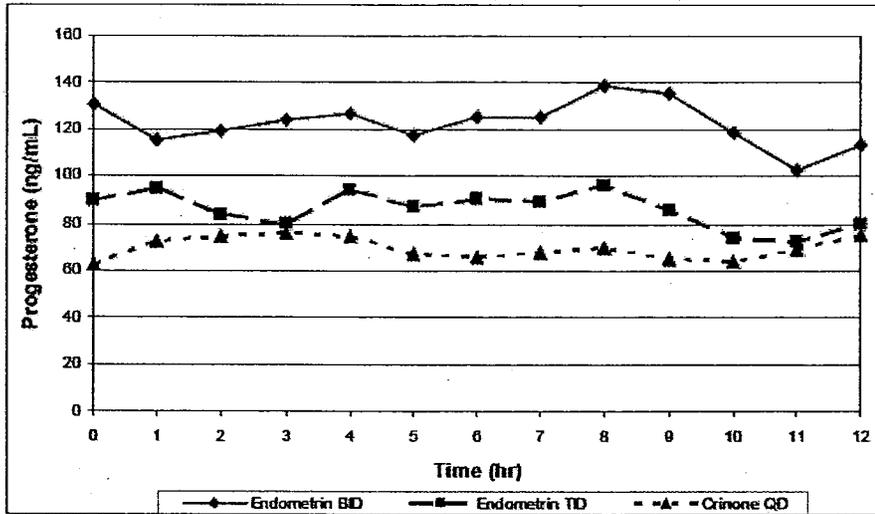
The maximum number of patients per mean datum were:
 Endometrin BID (N=3), Endometrin TID (N=3), Crinone 8% Gel (N=5)

Figure 13: Mean serum progesterone concentrations in IVF patients who became pregnant following ART



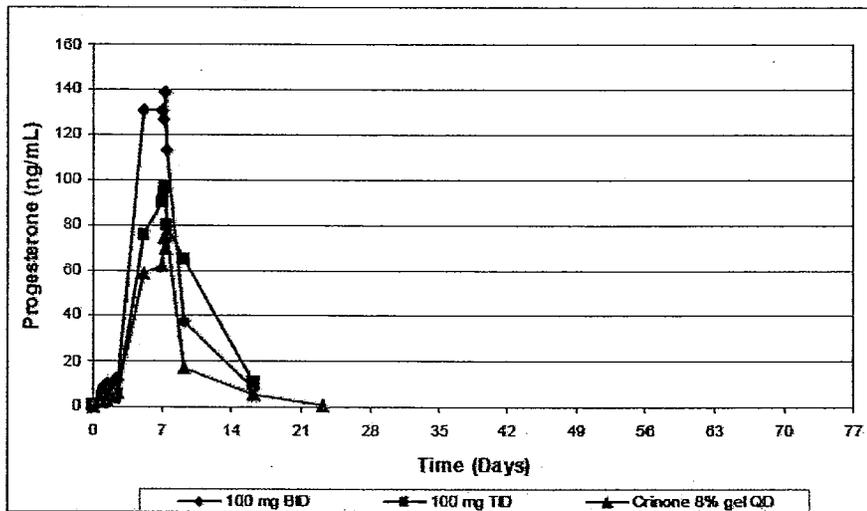
- In women who failed to achieve pregnancy, serum progesterone concentrations declined rapidly over the 7 to 14 days following treatment initiation suggesting a declining contribution from the initial hCG injection. Since, non-pregnant subjects were discontinued from the study no PK data was available after 14 days.

Figure 14: Mean day 7 serum progesterone concentrations in IVF patients who did not become pregnant in study 2004-02



The maximum number of patients per mean datum were:
 Endometrin BID (N=3), Endometrin TID (N=4), Crinone 8% Gel QD (N=5)

Figure 15: Mean serum progesterone concentrations in IVF patients who did not become pregnant following ART



- By the 4h time point on the day 16 (14th day of drug treatment), concentrations in non-pregnant women reached on average 7.95, 11.2 and 5.76 ng/ml, for Endometrin 100 mg BID, Endometrin 100 mg TID and Crinone 8 % gel QD, respectively. Since day 16 would be the onset of menses in subjects who did not conceive, endogenous progesterone production is likely to be minimal and progesterone levels may reflect the contribution of the exogenous treatments.
- *Reviewer conclusions: Treatment related differences in progesterone concentrations could not be identified from the PK subset in 2004-02. Limited data available from n = 2-3 per treatment at a single time point (4 hours) on day 16 in non-pregnant subjects of the phase 3 clinical trial 2004-02 suggest exposure similar to that observed in non-IVF volunteers of earlier studies; However, the*

usefulness of this data is limited as the relationship between concentrations at a single time point with the overall AUC is not understood.

2.2.5.3 What are the characteristics of drug absorption?

- Peak serum progesterone concentrations occurred at approximately 8-12 hours post-dose following single vaginal doses of Endometrin® tablets at various doses. Comparison of systemic exposure from the Endometrin® vaginal tablets to that of IM progesterone (50 mg) suggests a relative bioavailability of 8 %. High tissue concentrations of progesterone were achieved in the uterine endometrium following vaginal administration compared to IM progesterone that had very low uterine tissue concentrations.

2.2.5.4 What are the characteristics of drug distribution?

- In blood, progesterone is largely (95-98%) bound to plasma proteins. The 3 primary progesterone-binding proteins in plasma are albumin, cortisol-binding globulin (CBG), and sex hormone-binding globulin (SHBG), with albumin being the predominant progesterone-binding protein. During the follicular phase of the menstrual cycle in normal women, 2.4% of progesterone is unbound, 0.6% is bound to SHBG, 17.7% is bound to CBG, and 79.3% is bound to albumin. During the luteal phase of the cycle, progesterone concentrations increase approximately 40-fold; however, the percentage of progesterone bound to each protein remains the same.
- The metabolic clearance rate (MCR) for progesterone has been determined throughout the menstrual cycle. The MCR is estimated at 2490 ± 177 L/day during the follicular phase of the cycle (cycle days 2-12) and at 2460 ± 204 L/day during the luteal phase. The production rate for progesterone has been estimated to be 0.75-2.50 mg/day during the follicular phase and 15-50 mg/day during the luteal phase. The significantly higher rate of production of progesterone in the luteal phase does not affect the MCR.

2.2.5.5 What are the characteristics of drug metabolism?

- Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanones. Pregnanediols and pregnanones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization. While reductive processes are suggested to be primarily responsible for progesterone metabolism, there is some literature evidence to suggest oxidative metabolism

by CYP3A4, CYP2C19 and CYP2C9 (Swinney et al, 1990; Yamazaki et al, 1997).

2.2.5.6 What are the characteristics of drug excretion?

- Progesterone undergoes renal and biliary elimination. Following injection of labeled progesterone, 50-60% of the excretion of metabolites occurs via the kidney; approximately 10% occurs via the bile and feces. Overall recovery of the labeled material accounts for 70% of an administered dose, only a small portion of unchanged progesterone is excreted in the bile.

2.2.5.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

- Serum progesterone concentrations increased in a less than dose-proportional manner during once daily (50 - 200 mg) and twice daily (100 - 200 mg) dosing regimens of Endometrin® vaginal tablets in study 2004-01. The 3 QD tablet treatment groups (50, 100 and 200 mg tablets) had Cavg ratios of 1:1.28:2.23 compared to their dosing ratios of 1:2:4. The BID doses had mean Cavg ratios of 1:1.11, while the dosing ratios were 1:2.

Table 12: WinNonlin derived average serum progesterone exposure across doses used in study 2004-01

	50 mg QD	100 mg QD	200 mg QD	100 mg BID	200 mg BID
Cmax	6.59	7.70	12.45	13.16	12.98
Cavg	1.91	2.45	4.25	7.47	8.31
AUC_TAU	45.89	58.90	102.11	89.61	99.67
AUCINF_obs	52.19	67.74	113.37	116.12	125.30

2.2.5.8 How do the PK parameters change with time following chronic dosing?

- In study 2004-01 and study 2005-08, twice daily (BID) regimens resulted in drug accumulation up to 2.0-fold with multiple dosing. In study 2005-08, on average up to 3.0-fold accumulation was observed for the TID regimen upon multiple dosing. Early onset of steady-state was documented in these multiple-dose studies by examination of pre-dose (trough) levels.

2.2.5.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

- Moderate to high inter-individual variability was observed in progesterone PK from Endometrin® vaginal tablets in healthy volunteers (40-50 % in study 2004-01, and 35-60 % in study 2005-08) and in patients (50-85 % in study 2004-02). While some of the variability could have resulted due to random variability within and among the small populations studied, pre-treatment interventions (e.g. GnRH agonist use) and the subsequent hormonal status of the subject would impact the progesterone PK.

2.3 Intrinsic Factors

- There was no significant effect of age and body weight on serum progesterone PK in healthy volunteers and in ART patients. There is insufficient information in the clinical trials regarding the effect of race on any of the PK parameters. Pediatric and geriatric PK is not relevant due to the indication sought and clinical trials with Endometrin® included patients 18-42 years of age.
- In the phase 3 PK subset, there was no significant correlation between progesterone PK and clinical response (i.e. pregnancy outcome).
- Age (< 35 years or 35-42 years), and ovarian reserve (FSH < 10 IU/ml or 10-15 IU/ml) had an effect on the pregnancy outcome in the phase 3 trial as seen from the medical officer's conclusions pertaining to this data:

Table 13: Ongoing pregnancy rate by age and basal FSH level

Ongoing pregnancy	Endometrin® 100 mg BID N=404	Endometrin® 100 mg TID N=404	Crinone® 8% gel QD N=403
Subjects < 35 years of age (N)	247	247	243
Ongoing pregnancy rate n (%)	111 (44.9%)	117 (47.4%)	108 (44.4%)
95% Confidence Interval (CI)	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference with Crinone®	0.5%	2.9%	
[95% CI lower bound for difference]	[-8.3]	[-5.9]	
Subjects 35-42 years of age (N)			
Ongoing pregnancy rate n (%)	157	157	160
95% Confidence Interval (CI)	45 (28.7%)	54 (34.4%)	62 (38.8%)
Difference with Crinone®	[21.7, 36.4]	[27.0, 42.4]	[31.2, 46.8]
[95% CI lower bound for difference]	-11.3%	-4.7%	
	[-22.5]	[-15.9]	
Subjects with FSH < 10 IU/L (N)			
Ongoing pregnancy rate n (%)	350	347	350
95% Confidence Interval (CI)	140 (40.0%)	150 (43.2%)	147 (42.0)
Difference with Crinone®	[34.8, 45.3]	[37.9, 48.6]	[36.9, 47.4]
[95% CI lower bound for difference]	-2.0%	1.2%	
	[-9.3]	[-6.1]	
Subjects FSH 10-15 IU/L (N)			
Ongoing pregnancy rate n (%)	46	51	49
95% Confidence Interval (CI)	16 (34.8%)	20 (39.2%)	23(46.9%)
Difference with Crinone®	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
[95% CI lower bound for difference]	-12.2%	-7.7%	
	[-31.8]	[-27.1]	

Source: Adapted from NDA 22-057/S-000, Final Report, Adapted from Table 17, page 65 and Table 14.2.2.2, page 190 of 7,469.

Clinical reviewer's comments:

- *No clinically significant differences in ongoing pregnancy rates in subjects with normal ovarian reserve (serum FSH < 10 IU/L) or subjects under 35 years of age are observed between the three treatment groups.*
- *Endometrin® at the twice daily and three times daily appears to be clinically (and statistically) inferior in terms of ongoing pregnancy rates for subjects over 35 and/or for those with poor ovarian reserve compared to Crinone®. At the*

twice daily dosing, the difference is over 10% and is therefore insufficient for luteal supplementation in these patient groups. Therefore, the reviewer agrees with the Sponsor that based on this information, that subjects > 35 years of age and/or with poor ovarian reserve (FSH > 10 IU/L)

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- Hepatic impairment: No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. Since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated.
- Renal impairment: Because the majority of progesterone metabolites (50-60 %) are eliminated via the kidney, it is likely that renal impairment could result in accumulation of these metabolites. The implication of this is not known. The package insert for Prochieve® vaginal gel (progesterone 8 %) also approved for use in ART, does not contraindicate or warn against its use in renal impairment.

2.4 Extrinsic Factors

2.4.1 Drug-drug interaction potential

- No formal drug-drug interaction studies were conducted with Endometrin® vaginal tablets. While metabolism of progesterone is thought to occur primarily via reduction processes, there is literature evidence to indicate oxidative metabolism by CYP3A4, CYP2C19 and to some extent CYP2C9 (Swinney et al, 1990; Yamazaki et al, 1997).
- There are no in vivo DDI studies to document that enzyme inhibitors can cause increased plasma levels of progesterone. In vitro data by Swinney et al showed that the metabolism of progesterone in human liver microsomes was inhibited by Ketoconazole. Due to the potential involvement of CYP450s, there is at least a theoretical likelihood that enzyme inhibitors may alter the metabolism of progesterone. Sponsor suggests that increased serum progesterone levels due to concomitant administration of an enzyme inhibitor may not be a clinically relevant concern as formulations of progesterone that result in higher serum levels than Endometrin (eg.. IM progesterone) are currently approved for use in ART.
- The likelihood of an enzyme inducer increasing the clearance of Endometrin is also theoretical. There are no reports in the literature that suggest that enzyme

inducers can alter therapeutic progesterone levels achieved in ART by IM, oral or vaginal administration. The sponsor suggests that due to the vaginal administration of Endometrin tablets, a route that is expected to circumvent liver first pass effect and result in increased uterine drug delivery, the dependence of this product's efficacy on serum levels may be less compared to oral or IM products. However, this theory can be neither supported nor negated at this point due to absence of conclusive data.

- The likelihood of a clinically relevant effect of progesterone on the metabolism of concomitant medications appears to be low as literature survey did not yield in vivo evidence of such interactions. There is some information to suggest that in vitro, at concentrations much higher than seen for vaginal Endometrin, progesterone inhibits CYP2C19 and CYP2C9. The clinical relevance of such data is not known.
- The product information for the intravaginal products, Crinone and Prochieve, does not contraindicate concomitant treatment with any drugs, nor were any formal drug-interaction studies conducted with these products.
- The following statement appears in the proposed draft labeling for Endometrin: "Drug Interactions: T

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- Effect of concomitant vaginal products: Due to a potential concern that concomitantly applied vaginal products such as antifungals may interfere with or alter the dissolution characteristics of the Endometrin effervescent vaginal tablets, the sponsor was asked to address this issue. Ferring did not conduct a study to address this potential concern, however proposed to T

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The following statement was included in the proposed physician labeling under Section 4- Contraindications:

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Reviewer comments: Since the proposed indication for Endometrin® (approximately 10 weeks of use during ART) precludes use over an indefinite duration, avoiding concomitant use of other vaginal products while on this drug, may adequately address the issue.

2.5 Analytical methodology

- Serum progesterone concentrations were measured by _____ using a validated radioimmunoassay. After extraction, samples were incubated for two hours with an antiserum raised in rabbits against a progesterone-3-oxime-BSA conjugate and ¹²⁵I progesterone derivative. Separation of free and antibody bound progesterone was achieved by ammonium sulfate precipitation.

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- After gamma counting, the progesterone content of each sample was calculated using a standard curve derived from concentrations of purified progesterone ranging from : _____

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Validation parameters:

- The sensitivity of the assay (lowest measurable quantity of the analyte) was _____ ng/ml.
- The intra-assay and inter-assay precision for this method was _____ and the overall accuracy (% bias) ranged over _____
- The extraction efficiency was _____
- Samples were stable (average _____ of control) after 3 cycles of freeze and thaw.
- A test of linearity on sample dilution suggests good linearity over a 10-fold range.
- Cross Reactivity: Cross-reactions were determined by direct incubation of similar steroids with the antibody. Cross-reactivity was low as shown below:

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Table 14: Crossreactivity of progesterone antisera to various steroids

Steroid	Percent cross-reaction
Androstenedione	0.06
Corticosterone	0.1
Cortisol	<0.1
Dehydroepiandrosterone (DHEA)	0.03
Dihydrotestosterone	0.04
11-Desoxycortisol	0.03
Dexamethasone	<0.01
Estradiol	<0.01
Estriol	<0.01
17-Hydroxypregnenolone	0.06
17-Hydroxyprogesterone	0.3
20a-Hydroxyprogesterone	0.7
5a-Pregnane-3, 20-Dione	30
Prednisolone	<0.01
Prednisone	<0.01
Pregnanediol	<0.01
Pregnanetriol	<0.01
Pregnenolone	7.0
Testosterone	0.07

- The expected ranges of progesterone in adult females are given in this method validation report as 0.15-0.7 ng/ml (mean = 0.32 ng/ml) during the follicular phase, and 2 – 25 ng/ml (mean = 7.5) during the luteal phase.

3 Labeling

OCP recommended labeling changes are shown:

HIGHLIGHTS OF PRESCRIBING INFORMATION

Warnings and Precautions:

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.1 OCP filing review

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-057	Brand Name	Endometrin®	
OCP Division (DCP 1,2,3,4 or5)	DCP 3	Generic Name	Progesterone (micronized)	
Medical Division	DRUP	Drug Class	Steroidal hormone	
OCP Reviewer	Sandhya Apparaju	Indication(s)	Pregnancy through Progesterone supplementation as part of Assisted Reproductive Technologies (ART)	
OCP Team Leader	Ameeta Parekh	Dosage Form	Effervescent Tablets	
		Dosing Regimen	100 mg b.i.d. or 100 mg t.i.d.	
Date of Submission	08/21/2006	Route of Administration	Vaginal	
Estimated Due Date of OCP Review	04/20/2007	Sponsor	Ferring Pharmaceuticals	
PDUFA Due Date	06/21/2007	Priority Classification	Standard	
Division Due Date				
Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Label is submitted in the new SPL format
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
4.2 <i>Healthy Volunteers-</i>		2		SD and MD PK from nonfasting pharmacokinetic studies of Study 2004-01 and 2007-01
single dose:	X			
multiple dose:	X			
4.2.1 <i>Patients-</i>				SD and MD PK from clinical trial patients undergoing PK in Study 2006-01, Submission
single dose:	X			
multiple dose:	X			
Dose proportionality -				from Study 2002-01
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				No specific DD studies were conducted. Literature reviewed indicates no known drug-drug interactions. Metabolic pathways and the potential for drug-drug interactions are discussed in the NDA.
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				Female indication
pediatrics:				Not applicable
geriatrics:				Indication specific
renal impairment:				
hepatic impairment:				Contraindication
PD:				
Phase 2:	X		1	PK/PD study 2004-01; PD assessments include endometrial biopsy measures including thickness, drug concentrations in endometrium, conversion to secretory state from a proliferative state. Dose selection was based on this phase 2 assessment of PD.
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:		X	1	PK/PD study 2004-01; healthy female volunteers;
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X		1	PK subgroup in clinical trial 2004-02
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				Compared to the progesterone reference study 2004-01.
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				No in vivo BE studies were conducted as the formulation and manufacturing did not change during development.
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				Not relevant for vaginal route
Dissolution:	X			Submitted in CMC (module 3); Proposed release specification: NLT C_{50} (Q) at 20 minutes.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				

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Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 22-057
Compound: Micronized Progesterone
Sponsor: Ferring pharmaceuticals
Date: 09/26/2006
Reviewer: Sandhya Apparaju

Background: Ferring Pharmaceuticals has submitted a 505 b (1) application (NDA 22-057) for Endometrin®, an effervescent vaginal tablet of micronized progesterone (100 mg), for progesterone supplementation as part of Assisted Reproductive Technologies (ART).

Progesterone is a natural, endogenous hormone released from the ovary during the menstrual cycle and is necessary for embryo implantation and successful establishment and maintenance of pregnancy.

Progesterone supplementation is a standard part of infertility treatment. The sponsor is proposing a BID and a TID dosing regimen using 100 mg Progesterone vaginal tablets _____ for progesterone supplementation.

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Three clinical pharmacology studies have been submitted in this NDA (Study 2004-02 is a large clinical trial that had a PK substudy):

1. Study 2004-01: A Randomized, Open-Label, Pharmacokinetic, Pharmacodynamic and Tolerability Study of Three Dosage Strengths and Two Administration Regimens of a Vaginal Micronized Progesterone Tablet (Endometrin®) in Healthy Pre-menopausal Female Subjects.
2. Study 2005-08: A Randomized, Open-Label, Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) compared to Crinone 8% Vaginal Gel in Healthy Pre-menopausal Female Subjects.
3. Study 2004-02: A Multi-Center, Randomized, Open-Label, Parallel Group Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) Compared to Crinone 8% Vaginal Gel in Female Patients Undergoing In-Vitro Fertilization (IVF).

Pharmacokinetics: Single dose and multiple dose pharmacokinetics of Endometrin vaginal tablets were evaluated across different doses and dosage regimens in the completed clinical pharmacology studies. 50 mg, 100 mg and 200 mg doses were evaluated in various regimens including QD, BID or TID across these studies and in comparison to other approved formulations (i.m. injection and vaginal gel).

Systemic exposure from the vaginal tablets appears to be lower than that observed following IM injection of progesterone and higher than that observed with the approved vaginal gel (Crinone). Systemic exposure from the vaginal tablets also increased in a less than dose-proportional manner with increasing doses.

(Note: Baseline or endogenous progesterone levels in these subjects were less than 1 ng/ml due to hormone down-regulation following GnRH agonist injection; all drug concentrations for PK analysis were also corrected for baseline progesterone).

Population PK data: In addition, population PK study report from a subgroup of the target population (healthy pre-menopausal women undergoing IVF) in the clinical trial 2004-02 is included in the NDA. In this study, the exposure from vaginal administration of micronized progesterone appears to be markedly higher than that observed in healthy pre-menopausal females of study 2005-08; the sponsor attributes this to the increase in the endogenous production of progesterone initiated by IVF treatment; by day 16 in those women that did not become pregnant, these levels declined to what was observed in the healthy population, while in women who became pregnant, the systemic levels of progesterone continued to be high throughout the 10 week treatment period.

(Note: Primary medical reviewer Dr. Gassman acknowledged that IVF treatment can result in high progesterone levels than those observed during the release of a single follicle).

Pharmacodynamics: Study 2004-01 conducted in healthy, pre-menopausal women also evaluated the effect of treatment on various PD endpoints including endometrial tissue concentrations of progesterone, endometrial thickness, and secretory status of the endometrium. Dose-response information obtained from this study was utilized to justify dose selection for the larger clinical trial of Endometrin in women undergoing IVF.

The following conclusions appear in the final report for PK/PD study 2004-01: "A no-effect dose (≤ 100 mg QD) was established and a dose-response was demonstrated".

Drug-interactions: No specific drug-interaction studies were conducted with Endometrin. However, in response to a request from FDA, the sponsor has provided a comprehensive literature review to address progesterone metabolism (metabolic pathways, enzymes involved and the potential for drug-drug interactions).

(Note: The sponsor was asked to address the effect of concomitant vaginal preparations in presence of Endometrin during the EOP2 meeting; While no formal studies were conducted to address this, the sponsor did include the following statement in the draft label under the patient counsel information section: "_____

Medical officer, Dr. Gassman considers that this important issue needs to be addressed since other vaginal preparations for example antifungal creams for Yeast infections may be used concomitantly in pregnancy; this will be a review issue).

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Food-effect: While food has been shown to increase the bioavailability of oral progesterone, due to the vaginal route of administration for Endometrin, food-based interactions are not relevant.

Special populations:

- Geriatric: PK, safety and effectiveness in geriatric patients (>65 years) have not been assessed. This indication is for normal ovulatory, pre-menopausal women undergoing IVF.
- Liver dysfunction: Drug is contraindicated in women with hepatic dysfunction or disease.
- Renal impairment: Progesterone metabolites are excreted in urine; renal impairment is not currently proposed as a contraindication for Endometrin use.
- Pediatric: Since pregnancy through ART is not a pediatric indication, a waiver has been requested.

(Note: While renal impairment patients were not included in the clinical trials, this however is not a proposed contraindication for Endometrin and will need to be addressed during review).

Intrinsic factors: Data on intrinsic factors (age, race, body mass index, ovarian reserve, infertility diagnosis) were collected as they related to infertility treatment success and safety during the clinical trial 2004-02.

QT prolongation: No thorough QT studies have been conducted for Endometrin; Progesterone is an endogenous steroidal hormone and the proposed therapy aims at replacement therapy in progesterone-deficient individuals. Other formulations (i.m.) that result in higher systemic concentrations than those seen with Endometrin are currently approved.

Analytical methods: Methodology and validation reports could not be located; this information (or its location in the NDA) will be requested from the sponsor.

Clinical vs. to-be-marketed formulations: The proposed commercial formulation is identical to that used for the Phase 1/2 and 3 clinical trials. The sponsor claims that "Since the formulation and manufacturing process were not changed throughout the clinical development program, no comparative in-vivo study was conducted in the development of Endometrin@.

Recommendation:

The Office of Clinical Pharmacology /Division of Clinical Pharmacology III find that the Human Pharmacokinetics and Bioavailability section for NDA 22-057 is filable.

Sandhya Apparaju, Ph.D., Primary Reviewer

09/29/2006

Ameeta Parekh, Ph.D., Team Leader

09/29/2006

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandhya Apparaju
5/21/2007 09:29:28 AM
BIOPHARMACEUTICS

Myong-Jin Kim
5/24/2007 02:31:15 PM
PHARMACOLOGIST