CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-843

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 15 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: 20-843

Compound: Prometrium™ (100 mg progesterone capsules)

Sponsor: Schering Corporation

Type of Submission: Original NDA

Date of Submission: March 10, 1997

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

Background:

This original New Drug Application (NDA 20-843), was submitted by the Schering Corporation on March 10, 1997, in support of their product, Prometrium® (progesterone, USP) 100 mg capsules. This product is to be administered orally for the prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets. To support the efficacy and safety of Prometrium® for the above indication, the sponsor submitted data from one controlled Phase III clinical study. This study was sponsored by the National Institute of Health (NIH), and conducted by the PEPI (Post-menopausal Estrogen/Progestins Interventions) Group.

Many sections of NDA 20-843 make reference to NDA 19-781 (Prometrium® Capsules for use in Secondary Amenorrhea) originally submitted on September 30, 1987, and amended on February 8, 1996. In a meeting with the Agency on November 1, 1996, the sponsor agreed to conduct a drug-drug interaction study between Prometrium® and Premarin®. The results of this study were not required at the time of submission, however, the study had to be initiated at the time of filing and the final report had to be submitted at least 90 days before the goal date for NDA 20-843 (March 11, 1998). The draft protocol for this study was discussed with the Agency on February 4, 1997 and March 6, 1997. As of this date (January 13, 1998), no data from the drug interaction study have been submitted.

Comments:

1. NDA 20-843 makes reference to Studies C91-259-01 and C91-255-01, submitted to NDA 19-781. Study C91-259-01 evaluated dose proportionality and multiple dose

pharmacokinetics of Prometrium in healthy male volunteers; Study C91-255-01 evaluated the effect of food on the oral bioavailability of Prometrium (also in healthy male volunteers). Both studies have been reviewed and commented on by Dr. K. Gary Barnette (see Attachment A).

2. To date, the sponsor has not submitted any data from the drug-drug interaction study as was agreed upon in a meeting with the Agency on November 1, 1996.

3. The labeling (Attachment B) is acceptable provided the relative bioavailability comparison to an intramuscular injection under the **Pharmacokinetics/*Absorption*** section is deleted. This was originally requested by Dr. K. Gary Barnette who reviewed the relevant studies and judged them to be inadequate. The labeling may be modified further pending the results of the drug interaction study.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-843, submitted on March 10, 1997. Based on the review of the pharmacokinetic and biopharmaceutics studies referenced in NDA 19-781, OCPB/DPEII finds this NDA acceptable, pending submission of data from the drug-drug interaction study agreed upon during the November 1, 1996 meeting with the Agency. Additionally, the labeling may be modified based on the results of drug interaction study.

/S/

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

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 1/13/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 1/15/98

cc:
NDA 20-843
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (D. Moore, T. van der Vlugt)
CDR (Barbara Murphy For Drug)

Attachment A

NDA 20-843

Includes:
Clinical Pharmacology/Biopharmaceutics Review

of NDA 19-781, dated August 7, 1996

AUG 7 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 19-781

Compound: Prometrium® (100 mg micronized progesterone soft gelatin capsule)

Submission Dates: 2/8/96 (Amendment Serial No. AZ)
6/14/96 (Amendment Serial No. BB)

Sponsor: Schering Corporation

Type of Submission: NDA Amendment(response to non-approval letter)

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

Synopsis:
NDA 19-781 was submitted to the FDA on September 30, 1987 by Besins Pharmaceuticals and resubmitted by LaSalle Laboratories, the US affiliate of Besins-Iscovesco Pharmaceuticals, Inc. The indication for micronized progesterone under NDA 19-781 is the treatment of secondary amenorrhea (cessation of menses in a woman who has previously menstruated). A non-approval letter was issued by the Agency on August 17, 1990. A copy of this letter is included in Attachment 1. On July 23, 1991 a meeting addressing the non-approval letter was held. The sponsor agreed at that time to conduct two pharmacokinetic studies to evaluate the dose proportionality and the effect of food on Prometrium® kinetics. The current submission contains the response to each of the biopharmaceutic comments in the deficiency letter

as well as the results of the dose proportionality study and food effect study (previously reviewed by DPE II, March 26, 1993) that were agreed upon by the Agency on July 23, 1991.

Teleconferences between Dr. Lechner of Schering Corporation and this reviewer and Dr. Banfield, Dr. Lechner, Ms. Matlosz and Ms. Salfi of Schering Corporation and this reviewer were held on March 15 and 21, 1996, respectively. The sponsor submitted additional information in response to these teleconferences in the form of an amendment (Serial No.BB) to NDA 19-781 on June 14, 1996. The review of this submission is also included in this document. Also included herein is the proposed package insert (Attachment 2).

It should be noted that the name Prometrium® (the latest proposed name) is synonymous with Utrogestan as this NDA has changed hands during the course of development as has the name.

Background:

The oral administration of micronized progesterone for ten days to premenopausal women with secondary amenorrhea is intended to induce withdrawal bleeding. The cause of the bleeding is progestational activity in endometrial secretory phase transformation. This was reportedly confirmed in a study in which Prometrium® significantly induced secretory changes in women compared to placebo (study not submitted at this time, therefore not reviewed herein).

A summary of the pharmacokinetic studies previously submitted to NDA 19-781 is presented in Table 1 and a summary of the pharmacokinetic studies submitted on February 8, 1996 is included in Table 2.

Table 1: Summary of PK Studies Previously Submitted to NDA 19-781

Study #	Study Design	n	Sex (m/f)	Race (w/b)	Mean Age (range)	Treatment Dose, Dosing Frequency
Study 1 T91-005	Randomized, Open-label, Crossover	15	0/15	14/1	51	Placebo Fast: 2 x 100 mg, QD x 5d Fed: 2 x 100 mg, QD x 5d
Study 2 T91-004	Randomized, Open-label, Crossover	15	0/15	14/1	52	1 x 100 mg, QD x 5d 2 x 100 mg, QD x 5d 3 x 100 mg, QD x 5d
Study 3 T91-003	Randomized, Open-label, Crossover	15	0/15	14/1	53	Utrogestan: 2 x 100 mg, QD x 2d Progesterone: 50 mg IM, QD x 2d

▸ These studies were not submitted to the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II at this time. Thus, reviews of these studies are NOT contained herein.

Table 2: Summary of PK Studies Submitted to NDA 19-781 on 2/8/96

Study #	Study Type	Study Design	n	Sex (m/f)	Race (w/b)	Mean Age (range)	Dose, Dosing Frequency
C91-259	Dose Escalation	Randomized Open-Label Crossover	25	25/0	18/7	32	* 1x100mg, QDx7d * 2x100mg, QDx7d * 3x100mg, QDx7d * 4x100mg, QDx7d
C91-255	Food Effect	Randomized Open-Label Crossover	24	24/0	17/4 1 Asian 2 others	23	* Fasted 3x100mg * w/Food 3x100mg * 2h p/Food 3x100mg * 4h p/Food 3x100mg

The results and conclusions from Study 1 (T91-005) and Study 2 (T91-004) conducted by the previous sponsor of this NDA, Besins Pharmaceuticals, were dismissed due to inadequate sampling times. Food effect and dose proportionality studies have been "re"-run and are or have been submitted for review. Study 3 (T91-003), a

relative bioavailability study has been previously reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and is further commented upon herein.

Sponsor's Response to Deficiencies in Letter of August 17, 1990: Complete documentation of the sponsor's response to deficiencies outlined in the non-approval letter issued by the Agency on August 17, 1990 is included in Attachment 3.

Reviewer's Comments on Sponsor's Response to Deficiencies (non-approval letter dated August 17, 1990):

Bioavailability and Bioequivalence:

2a. The response is adequate.

2b. The sponsor has conducted Study C91-255 (food effect study) and C91-259 (multiple dose, dose proportionality study) to address the insufficiencies outlined in comment 2b. The review of these studies is contained herein (Attachment 4).

2c. I have not reviewed nor reanalyzed the raw data from Study 3. This should be unnecessary due to previous review. However, from the sponsor's analysis, since the elimination phase of the IM dose was missed and the portion of the curve being used to extrapolate to AUC_∞ may include the distribution phase of progesterone, the calculation of AUC_∞ is inaccurate. Therefore, a bioavailability analysis between the IM and oral doses of micronized progesterone is not appropriate with available data.

2d. Once again in Study 3, the calculated AUC_∞ after IM dosing is probably inaccurate (see Comment 2c, above). Therefore only the Cmax value is evaluable and no sequence, subject or phase effect was observed on this parameter. ANOVA was used in Studies C91-255 and C91-259 to determine the effect of phase, subject and treatment on the pharmacokinetic parameters. Only the treatment showed a consistent statistically significant effect. However, probably due to high interindividual variability in progesterone kinetics, a subject effect was seen in some parameters.

2e. The response is adequate.

2f. The response is adequate.

2g. The response is adequate.

2h. An appropriate study has been completed and reviewed to assess the effect of a high fat meal on the pharmacokinetics of a 300 mg dose. Study C91-255 utilized a 3x100mg dose of Prometrium® and a food effect was observed and is included in the labeling under the section entitled, *"Food-Drug Interaction"*.

Labeling:

3a. The response is adequate.

3b. The response is adequate. However, according to current regulations, a request was made in a teleconference between this reviewer and Dr. Lechner, Schering Laboratories, on March 14, 1996 the Clinical Pharmacology section under the major heading Pharmacokinetics be reformatted into the subheadings; Absorption, Distribution, Metabolism and Excretion with a Special Population section detailing the PK in renally impaired, hepatically impaired and obese populations. The reformatted labeling was promptly submitted and is included in Attachment 2.

3c. The response is adequate.

3d. The response is adequate.

3e. The response is adequate.

3f. The response is adequate.

Biopharmaceutic Comments:

1. The response is adequate.

2. The response is adequate.

3. The response is adequate.

4. The response is adequate.

5. Study C91-255, a food effect study was conducted and submitted to the FDA on February 8, 1996. The review of this study is included in Attachment 4.

Teleconferences:

- A teleconference was held with Dr. Banfield, Dr. Lechner, Ms. Matlosz and Ms. Salfi of Schering Corporation on March 21, 1996. The following comments and question were made by this reviewer.

1) In Study C91-259, Subject 24 had AUC and Cmax values >10 fold higher than the mean values of the other subjects studied. The quality control samples, blood sample collection, analysis and handling as well as the demographics and adverse events from this study should be evaluated for possible explanations for the unusual parameters observed in Subject [redacted].

2) Analysis for a body weight effect on the pharmacokinetics of Prometrium® should be submitted.

3) Do women experiencing secondary amenorrhea have lower progesterone levels than normal women?

Sponsor's Response to Comments and Questions of March 21, 1996:
Complete responses are included in Attachment 5.

Reviewer's Comments:

1) With the exception that Subject [redacted] was the youngest of all subjects studied, none of the suggested analyses or reevaluations (quality control, blood sampling and handling, demographics and adverse events) yielded a valid explanation for the high systemic exposure (AUC and Cmax) observed in this subject.

2) There does not appear to be a correlation between body weight and AUC or Cmax. However, it should be noted that the range of weights included in the reported studies was lbs and no obese subjects were enrolled.

3) The sponsor states that, "progesterone levels are NOT routinely drawn in this setting". Therefore, I would conclude that it is not known if insufficient progesterone levels or a receptor binding phenomenon is the probable causative event leading to secondary amenorrhea.

- A teleconference between this reviewer and Dr. Lechner of Schering Corporation was held on March 15, 1996. It was requested that the Pharmacokinetic portion of the Clinical Pharmacology section of the proposed labeling be reformatted to include subsections of Absorption, Distribution, Metabolism, Excretion, and Special Populations. The revised labeling is included in Attachment 2.

Summary of Pharmacokinetic Studies Submitted 2/8/96 (Attachment 4)
A significant and comparable food effect was seen when Prometrium® was administered at the time of a meal and 2 hr after a meal (see Table 3). However, a further increase in bioavailability was

observed when dosing 4 hr after meal compared to all other treatments tested (fasting, with meal and 2 hr after meal).

Table 3: Mean (N=24) Pharmacokinetic Parameters of Progesterone

Parameter	Mean (%CV)			
	Treatment A (Fasted)	Treatment B (w/breakfast)	Treatment C (2 hr after meal)	Treatment D (4 hr after meal)
Cmax (ng/ml)	58 (125)	64 (122)	61 (93)	133 (86)
Tmax (hr)	2.0 (63)	3.3 (87)	3.5 (71)	2.0 (46)
AUC_∞ (ng×hr/ml)†	135 (90)	184 (69)	183 (60)	243 (58)
$t_{½}$ (hr)	13.0 (41)	13.6 (49)	13.6 (34)	16.9 (35)

† N=19, "due to high variability in progesterone concentrations in the terminal phase, $t_{½}$ and AUC_∞ could not be accurately determined in subjects

In Study C91-259 it was determined that dose proportionality could not be established in normal male volunteers between doses of 300 and 400 mg QD (see Table 4).

Table 4: Mean (N=24) Steady-State Pharmacokinetic Parameters of Progesterone

Parameter	Mean (%CV)			
	Treatment A (1x100 mg QD)	Treatment B (2x100 mg QD)	Treatment C (3x100 mg QD)	Treatment D (4x100 mg QD)
Cmax (ng/ml)	9.85 (137)	22.8 (179)	40.7 (178)	47.0 (132)
Tmax (hr)	2.94 (70)	2.85 (63)	3.00 (61)	2.42 (78)
AUC0-24 (ng×hr/ml)†	38.5 (109)	87.0 (163)	157 (165)	180 (112)
$t_{½}$ (hr)‡	17.2 (23)	17.0 (33)	16.8 (35)	16.0 (32)

† AUC_{0-24} at steady-state is also AUC(τ) where τ represent the dosing interval.

‡ N=22, due to variability in progesterone concentrations in the terminal phase, $t_{½}$ could not be calculated for subjects

However, Subject in Study C91-259 had AUC_∞ and Cmax values almost 10 times higher than the mean of all subjects (n=24, see Table 5, below). There is no explanation for this observation. It should be noted that these subjects were male and fasting (the recommended target population is pre-menopausal women with secondary amenorrhea and recommended dosing is with food). According to study C91-255, a statistically significant increased bioavailability is seen with food. Therefore, in a female patient (lower body weight) with this type of absorption profile and dosing with food, the amount of systemic exposure of progesterone may be much higher.

Table 5

	AUC ng*h/ml				Cmax ng/ml			
	1x100mg	2x100mg	3x100mg	4x100mg	1x100mg	2x100mg	3x100mg	4x100mg
Sub[redacted]	227.27	738.29	1340.13	1049.99	70.84	205.96	372.45	287.18
Mean (%CV)	38.53 (108.55)	86.98 (162.77)	156.68 (165.31)	180.27 (112.28)	9.85 (136.62)	22.81 (179.20)	40.65 (178.36)	47.02 (131.56)

Reviewer Comments:

1. The high systemic exposure to progesterone (AUC∞ ≈10 fold higher than the average of the other subjects included in Study C91-259) observed after all four doses (100, 200, 300 and 400 mg) in Subject [redacted] has been evaluated. However, no explanation for this phenomenon is readily available and Subject [redacted] can be considered an outlier.

- It should be noted that the t½ of this subject is comparable to that seen in other subjects (see Table 6). Therefore, the clearance of progesterone does not appear to be altered in this subject and is not the cause of the high systemic exposure seen in Subject [redacted].

Table 6. T½ (hr)

Dose	Subject [redacted]	Mean ± SD (n=23)
1 × 100 mg	22.52	16.89 ± 3.76
2 × 100 mg	14.66	16.77 ± 5.62
3 × 100 mg	11.18	17.50 ± 6.66
4 × 100 mg	14.39	15.85 ± 5.05

- Although the serum progesterone levels at time = zero (pre-dose) are higher than the average of the other 23 subjects this relatively small difference does not account for the high systemic levels observed in subject [redacted] (see Table 7).

Table 7. Cp (ng/ml) at Time = 0 (pre-dose)

Dose	Subject [redacted]	Mean ± SD (n=23)
1 × 100 mg	0.39	0.23 ± 0.10
2 × 100 mg	0.51	0.23 ± 0.12
3 × 100 mg	0.51	0.22 ± 0.11
4 × 100 mg	0.37	0.23 ± 0.10

- The blood and urine chemistries and demographics of Subject

[redacted] were generally within normal limits and the high systemic exposure seen in this subject could not be attributed to these data.

- The standard curve and quality control samples assayed with serum samples from Subject [redacted] were within the acceptable limits and re-analysis of various samples from this subject confirmed the comparatively high serum concentrations of progesterone.

- Although the absolute and relative bioavailability of Prometrium® is not known, it is apparent that it is low, probably less than 10%. Therefore, an alteration in absorption could result in serum levels 10 fold higher, but there is no obvious explanation for or proof of this phenomenon.

2. Linear pharmacokinetics do not appear to exist between the proposed doses of 300 mg QD and 400 mg QD (see Table 5, above), but the high inter-subject variability is acknowledged. It should be noted that the AUC and Cmax values of the 300 mg dose are markedly higher in subject [redacted] than those of the 400 mg dose. Since these numbers are so high compared to those seen in the other subjects, this alone may account for the appearance of non-linear kinetics over this portion of the dose range. An analysis of these data excluding subject [redacted] is included in Table 8 and indicates dose proportionality. Therefore, it is concluded that the lack of dose proportionality of Prometrium® in these 24 subjects is not due to the formulation and dose proportionality exists between doses of 100 and 400 mg.

Table 8

	Mean AUC (CV) ng*h/ml				Mean Cmax (CV) ng/ml			
	1x100mg	2x100mg	3x100mg	4x100mg	1x100mg	2x100mg	3x100mg	4x100mg
Includ. Sub[redacted]	38.53 (108.55)	86.98 (162.77)	156.68 (165.31)	180.27 (112.28)	9.85 (136.62)	22.81 (179.20)	40.65 (178.36)	47.02 (131.56)
Exclud. Sub[redacted]	30.3 (38.07)	58.7 (48.20)	105 (56.55)	142 (57.25)	7.20 (48.57)	14.8 (82.45)	26.2 (61.69)	36.6 (95.09)

3. Due to a food effect that exists at least up to 4 hours post prandial, the proposed dosing regimen is single daily doses of 300 mg or 400 mg WITH the evening meal for 10 days.

4. It is stated in the proposed labeling (page 3,

Pharmacokinetics, *Absorption*) that the relative bioavailability to IM injection is approximately 6%. However, as stated above the sampling times used to assess the plasma concentration versus time profile of progesterone after IM injection did NOT adequately assess the elimination portion of the curve. Therefore, AUC_∞ can not be accurately estimated and the aforementioned statement should be removed from the labeling.

5. It should be included in the labeling for this product that the pharmacokinetics of this formulation has NOT been assessed in subjects with weights outside the range of lbs and this testing was in males only. Therefore, neither obese nor individuals with low body weight have been assessed pharmacokinetically.

6. Since the pharmacokinetics of the 400 mg dose in the target population has not been assessed, the labeling should be amended to include data from the dose proportionality study in healthy male volunteers pending study of this dose in the target population.

Recommendation:
The amendment to the NDA 19-781 submitted to the Agency on February 8, 1996 and the supplement submitted June 14, 1996 have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II. Based on the clinical pharmacology and biopharmaceutics information from Studies C91-255 and C91-259 and the responses to the deficiency letter of August 17, 1990 it is recommended that approval of Prometrium® for the indication of 10 day treatment of secondary amenorrhea and the dosing regimen of 300 or 400 mg/day with the evening meal be granted. However the following additional recommendations are made, although not conditions for approval;

- If a labeling claim of the relative bioavailability of Prometrium® to an IM injection is desired, an appropriate study should be conducted, including proper sampling times.

- The sponsor should assess the pharmacokinetics of the 400 mg dose of Prometrium® in the target population and amend labeling to include these data.

- Pending approval of this application by the Division of Urologic and Reproductive Drug Products (HFD-580), The Office of Clinical Pharmacology and Biopharmaceutics requests the opportunity to review the product's final labeling prior to marketing.

The Recommendation and Comments 4, 5 and 6 should be communicated to the sponsor as appropriate.

/S/

K. Gary Barnette, Ph.D.
Division Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 8/5/96
FT signed by Angelica Dorantes, Ph.D., Team Leader 8/6/96

cc: NDA 19-781, HFD-580, HFD-580 (Cropp, Kish), HFD-870 (M.Chen, Hunt, Dorantes, Barnette), HFD-340 (Viswanathan), HFD-850 (Lesko), Drug File, Chron file, Reviewer (Clarence Bott, HFD-870), HFD-205 (FOI).

Attachment B

NDA 20-843

Proposed Labeling

Redacted 20

pages of trade

secret and/or

confidential

commercial

information

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: April 8, 1997

Place: PKLN 17B-43

To: HFD-580

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

RE: 21-Day Filing Meeting, **NDA 20-843,** PROMETRIUM® (Progesterone, USP) 100 mg Capsules.

Background:

NDA 19-781 for PROMETRIUM® was originally submitted on September 30, 1987, and amended on February 8, 1996. PROMETRIUM® (Progesterone, USP) for the treatment of secondary amenorrhea was deemed approvable in a letter issued on March 28, 1997. On March 10, 1997, PROMETRIUM® was submitted for a new indication: "prevention of endometrial hyperplasia in non-hysterectomized post-menopausal women who are receiving conjugated estrogens tablets", under NDA 20-843.

Comments:

1. The sponsor has stated in the March 10th submission that the proposed formulation, a soft gelatin capsule containing 100 mg of micronized progesterone suspended in peanut oil, is identical to the formulation used in NDA 19-781.

2. The sponsor was granted permission to make reference of the studies previously submitted under NDA 19-781; therefore, in NDA 20-843, the sponsor did not submit new data for these studies.

3. Human pharmacokinetics and bioavailability studies submitted under NDA 19-781 have been reviewed and commented on by K. Gary Barnette, Ph.D., August 7, 1996.

4. At the November 1, 1996 meeting, the sponsor was required to conduct a drug-drug interaction study between PROMETRIUM® and Premarin®. At that meeting, the FDA agreed that a final report on the study was not required for filing, but complete results were needed at least three months before the NDA's Goal Date.

5. A draft protocol for the drug interaction study (IND Study no. C96-417) was submitted December 23, 1996 and was reviewed and commented on by K. Gary Barnette, Ph.D., on January 22, 1997. The protocol was deemed adequate to assess the effect of PROMETRIUM® on the pharmacokinetics of Premarin®.

6. On February 12, 1997 a second draft of study no. C96-417 (IND was submitted and is currently under review. The amended protocol included the recommended changes requested during a teleconference on February 4, 1997 and Dr. Barnette's Comments on this protocol as conveyed by the Agency's letter dated January 30, 1997.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) is of the opinion that the provided information is appropriate to support the filing of NDA 20-843. The sponsor, however, should be reminded that the results of the drug-drug interaction study between PROMETRIUM® and Premarin® should be submitted for review as soon as they become available.

cc:
NDA 20-843
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (D. Moore, T. van der Vlugt)
CDR (Barbara Murphy For Drug)

Attachment

NDA 19-781

Includes:

Summary Table of Human Pharmacokinetics/Bioavailability Studies

Table F1. Human Pharmacokinetics/Bioavailability Studies of Oral Micronized Progesterone Capsules.

Study Title/Description	Study Number Investigator (Starting Date)	Number of Subjects[a]	Mean Age (Range)[b] Sex Distr. (M/F) Race Distr.[c]	Treatment Dose Dosing Frequency
A. Studies in Original NDA (19-781 Submitted 9/30/87 Effect of Food on the Absorption of Utrogestan from the Gastrointestinal Tract Following a Daily Dose of 200 mg for Five Days Type of Study: Randomized, Open-Label, Crossover Report Location: Vol: 1.3 Pgs: 406-740	Study 1 [T91-0051][d] Simon (9/15/86)	15	51 0/15 14W/1B	• Placebo 2 capsules QD x 5 Days • Utrogestan Fasted 2 x 100 mg QD x 5 Days • Utrogestan w/Food 2 x 100 mg QD x 5 Days
Dose Proportionality Following the Administration of Utrogestan in Doses of 100 mg, 200 mg and 300 mg once Daily for Five Days Type of Study: Randomized, Open-Label, Crossover Report Location: Vol: 1.3 Pgs: 406-740	Study 2 [T91-0041][d] Simon (11/3/86)	15	52 0/15 14W/1B	• Utrogestan 1 x 100 mg QD x 5 Days • Utrogestan 2 x 100 mg QD x 5 Days • Utrogestan 3 x 100 mg QD x 5 Days
Pharmacokinetics of Utrogestan 200 mg Administered Orally Once Daily for Two Days Compared to Progesterone in Oil 50 mg Administered Daily for Two Days Type of Study: Randomized, Open-Label, Crossover Report Location: Vol: 1.3 Pgs: 406-740	Study 3 [T91-0031][d] Simon (1/5/87)	15	53 0/15 14W/1B	• Utrogestan 2 x 100 mg QD x 2 Days • Progesterone in oil 50 mg IM QD x 2 Days

a: Healthy post-menopausal volunteers.
b: Years.
c: W=White, B=Black
d: Study numbers for these studies were changed to the numbers in brackets when Schering Corporation assumed ownership of the NDA fro micronized progesterone.

Table F1 (Cont'd). Human Pharmacokinetics/Bioavailability Studies of Oral Micronized Progesterone Capsules.

Study Title/Description	Study Number Investigator (Starting Date)	Number of Subjects	Mean Age (Range)[b] Sex Distr. (M/F) Race Distr.[c]	Treatment Dose Dosing Frequency
B. Studies in NDA 19-781 2/8/96 NDA Amendment SCH 961: A Study Evaluating the Pharmacokinetic Profile and Dose Proportionality of Progesterone After Administration of Prometrium® Capsules: A Four-Way Cross-Over Study in Normal Male Volunteers Type of Study: Randomized, Open-Label, Crossover Report Location: Vol: 2.15-2.16 Ref Tab: 2 Data Listings: Vol: 2.16 Ref Tab: 2 Pgs: 354-555	C91-259-01 Cohen (5/17/92)	25[d]	32 25/0 18W/7B	• Prometrium™ 1 x 100 mg QD x 7 Days • Prometrium™ 2 x 100 mg QD x 7 Days • Prometrium™ 3 x 100 mg QD x 7 Days • Prometrium™ 4 x 100 mg QD x 7 Days
SCH 961: A Study Evaluating the Effect of Food on the Oral Bioavailability of Prometrium®: A Four-Way Crossover Study in Normal Male Volunteers Type of Study: Randomized, Open-Label, Crossover Report Location: Vol: 2.14-2.15 Ref Tab: 1 Data Listings: Vol: 2.15 Ref Tab: 1 Pgs: 219-462	C91-255-01 Seibold (1/20/92)	24	23 24/0 17W/4B/2O/1A	• Prometrium™ Fasted 3 x 100 mg Single Dose • Prometrium™ w/Food 3 x 100 mg Single Dose • Prometrium™ 2 hr p/Food 3 x 100 mg Single Dose • Prometrium™ 4 hr p/Food 3 x 100 mg Single Dose

a: Normal male volunteers.
b: Years.
c: W=White, B=Black, O=Other, A=Asian
d: Includes 1 replacement; 24 completed