CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19-781

MEDICAL REVIEW(S)

OCT 8 1996

MEDICAL OFFICER REVIEW

Title and General Information

Medical Officer's Review:
NDA#: 19,781
Original Submission: September 30, 1987 by Besins Pharmaceuticals
Resubmitted: March 17, 1989 by LaSalle Laboratories
Resubmitted: February 8, 1996 by Schering Corporation
Medical Officer Review Completed: September 16, 1996
Medical Officer Review Revised: October 4, 1996

Drug Name:
Generic name: soft gel capsule formulation of natural micronized progesterone.
Proposed trade name: Prometrium Capsules (formerly Utrogestan Capsules) or SCH 961 Capsules.
Chemical name: micronized progesterone.

Sponsor: Schering Corporation. The original application was submitted September 30, 1987 by Besins Pharmaceuticals, and resubmitted March 17, 1989 by LaSalle Laboratories, US affiliate of Besins-Iscovesco Pharmaceuticals, Inc. (Besins Pharmaceuticals was dissolved on September 26, 1988.) Transfer of ownership of the NDA to Schering Corp. occurred on July 1, 1990.
A not approvable letter was sent to Schering Corporation August 17, 1990 **(Attachment 1)**. The sponsor's response is appended in **Attachment 2.** Subsequently, concurrence was reached between the FDA and Schering Corp. to address the deficiencies by: (1) conducting two pharmacokinetic studies (dose proportionality study and food effect study) in male volunteers to minimize intra- and inter-subject variability, and (2) an additional clinical trial to address the effectiveness of Prometrium on inducing endometrial secretory transformation in postmenopausal women with proliferative endometrium induced by estrogen priming.

Pharmacologic Category: steroid hormone.

Proposed Indication(s): The treatment of secondary amenorrhea in premenopausal women.

Dosage Form, Duration and Route of Administration:

Important Related Drugs: There are no other oral-progesterone drug products currently approved. Medroxyprogesterone acetate is the most commonly prescribed

synthetic oral progestational drug product.

Related Reviews:
Dr. Ridgely C. Bennett's Medical Officer's reviews of NDA 19,781 dated August 4, 1989, January 18, 1990, and February 2, 1990.

Related INDs:
IND of Schering Corp. for oral micronized progesterone

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Material Reviewed
In addition to the clinical data submitted by the applicant, there is a significant amount of medical literature on the clinical use of oral progesterone which was reviewed as background material. The following citations represent the current most relevant publications. The sponsor has not made any claims based on these references.

The Writing Group for the PEPI Trial JAMA 273:199, 1995
The Writing Group for the PEPI Trial JAMA 275:370, 1996
JT Hargrove, et.al. Obstet Gynecol 73:606, 1989
WS Maxson and JT Hargrove Fertil Steril 44:622, 1985
JT Hargrove, et.al. Am J Obstet Gynecol 161:948, 1989
JA Simon, et.al. Fertil Steril 60:26, 1993
P Affinito, et.al. Maturitas 20:191, 1995
MM Shangold, et.al. Fertil Steril 56:1040, 1991
A Dupont, et.al. Maturitas 13:297, 1991
E Darf, et.al. Maturitas 13:109, 1991
S Kim, et.al. Fertil Steril 65:323, 1996
DL Moyer, et.al. Fertil Steril 59:992, 1993
C Bourgain, et.al. Human Reproduction 5(5):537, 1990
P Devroey, et.al. Int J Fertil 34(3):188, 1989
G Lane, et.al. BMJ 287:1241, 1983
TA Ryder, et.al. Maturitas 22:31, 1995
RJB King and MI Whitehead Fertil Steril 46:1062, 1986
G Lane, et.al. Fertil Steril 45(3):345, 1986
JY Gillet, et.al. Maturitas 19:103, 1994

Chemistry/Manufacturing Controls Please see the separate review. No clinically relevant deficiencies were found.

Animal Pharmacology/Toxicology Please see the separate review. No clinically relevant deficiencies were found.

Clinical Background

Relevant human experience

Some of the recently published articles (English only) containing the largest clinical experience with oral micronized progesterone are as follows:

MM Shangold, et.al. Fertil Steril 56:1040, 1991
A Dupont, et.al. Maturitas 13:297, 1991
DL Moyer, et.al. Fertil Steril 59:992, 1993
JY Gillet, et.al. Maturitas 19:103, 1994
The Writing Group for the PEPI Trial JAMA 273:199, 1995
The Writing Group for the PEPI Trial JAMA 275:370, 1996

These articles represent experience with over 600 women treated with 100-300 mg of oral micronized progesterone from one month to five years for the indications of secondary amenorrhea

Foreign marketing experience

Micronized progesterone as Utrogestan® was first marketed in 1980 by Besins-Iscovesco Pharmaceuticals, Inc. Since that time it has been marketed in 26 countries for various indications including menstrual irregularities related to anovulation and dysovulation, luteal insufficiency, and postmenopausal hormone replacement therapy. The range of dosing for these indications is between 200-300 mg/day. It has been recommended that these daily doses be administered as a single dose, as well as in divided doses. In Belgium, Luxembourg, France Greece, Portugal, and Switzerland one of its indications is for menstrual irregularities (anovulation/dysovulation) which is probably similar to a secondary amenorrhea indication. The sponsor estimates that approximately units (1 unit = 30 capsules) have been sold worldwide between 1980 and 1995.

Human Pharmacology, Pharmacokinetics, Pharmacodynamics

The most striking observation is the significant intra and inter-subject variability in absorption of oral micronized progesterone. As a result of this variability, it is predicted that the clinical responses to Prometrium will also be variable.

Regulatory history and other relevant background information

In Sept 30, 1987 NDA 19,781 for Utrogestan capsules by Besins Pharmaceutical, Inc. was submitted.

The Medical Officer review dated November 20, 1987 stated that Utrogestan is not covered by the DESI regulations and that none of the submitted clinical studies supported the efficacy of the proposed doses of Utrogestan for the claimed indications. It was recommended that the NDA not be filed.

In a January 22, 1988 meeting with Besins Pharmaceutical representatives, the sponsor indicated they thought Utrogestan could be approved as a "paper NDA". The FDA responded that in a meeting 3 years previously with the sponsor the need for clinical trials had been indicated. The need for bioavailability studies and to determine the effective dose for their proposed indication was also discussed. The need for the sponsor to address the possible toxicity of progesterone administered orally was discussed since the first pass effect in the liver and possible lipid changes would be different from the IM route of administration. The need to perform clinical studies using the

proposed dose in the proposed population was again stressed. Finally, it was suggested that the sponsor seek outside consultation in designing their clinical studies.

Letter dated April 18, 1988 to Besins Pharmaceuticals noted the additional deficiencies of PK parameters, assay validation and *in vitro* quality control tests.

March 22, 1989 to LaSalle Laboratories acknowledged the resubmitted application dated March 17, 1989 for Utrogestan capsules, NA 19,781.

Letter to the sponsor dated May 31, 1989 stated the application was not approvable after review of the chemistry, manufacturing and controls information.

Statistical review dated 8-4-89 stated that 300 mg/day produced a greater proportion of withdrawal bleeding than placebo, but requested assurance that the sponsor did not discard any data.

Pharmacology and Toxicology review of 8-11-89 had no objection to approval of the NDA.

Medical Officer review of 1-18-90 recommended against approval since substantial evidence of efficacy was not documented. Only Utrogestan 300 mg/day, and not 200 mg/day, was more effective than placebo in inducing withdrawal bleeding. The study by Dr. Vargyas indicated that micronized progesterone at 200 mg/day x 14 days was not a good progestational agent, and did not satisfactorily transform proliferative endometrium into secretory endometrium. In addition, the report by Lane et.al. concluded that suboptimal effects on the endometrium were observed with daily doses of 100 mg and 200 mg, but that 300 mg daily *may be* effective for therapeutic purposes. No studies that supported an indication for abnormal uterine bleeding were submitted. No data were submitted to document that Utrogestan 300 mg/day would transform proliferative endometrium into secretory endometrium.

At the January 22, 1990 meeting with LaSalle Laboratories the above reviews were discussed and the sponsor was urged to withdraw the application.

January 29, 1990 letter to the sponsor indicated that a 30 day extension would be granted for this application.
February 2, 1990 Medical Officers review of LaSalle's submission dated 1-30-90 concluded the following: 1) The study by Dr. Vargyas of the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg/day for 14 days each

cycle was not a good progestational agent and did not satisfactorily transform proliferative endometrium into secretory endometrium, and 2) The two published articles submitted do not provide substantial evidence that micronized progesterone at a dose of 300 mg/day consistently transformed proliferative endometrium into secretory endometrium.

February 13, 1990 the FDA met with LaSalle Laboratories to review their response to the deficiencies identified 1-22-90. The FDA proposed discussing this drug at the upcoming Advisory Committee meeting, but the sponsor declined. Agreed upon conclusions were as follows: 1) LaSalle would provide literature documentation that 80% induction of withdrawal bleeding was as good as or better than the efficacy of other progestins; 2) Class labeling will not be used. The only indication will be the treatment of secondary amenorrhea, and the efficacy rate for the induction of withdrawal bleeding will be stated as will be the extent of secretory change; 3) The labeling will state that there is no evidence establishing the efficacy of this product for endometrial protection in a postmenopausal population; 4) The FDA recommended a cautionary statement be included that there is no (or insufficient) evidence regarding the safety of long-term use of this drug; 5) The labeling section describing the mode of action will be modified accordingly.

> **Medical reviewer's comment: No documentation was ever provided by the sponsor that an 80% induction of withdrawal bleeding was as good as or better than the efficacy of other progestins.**

Pharmacokinetic review of April 30, 1990 listed fifteen deficiencies/recommendations.

June 21, 1990 review of Chemistry and Manufacturing Controls identified two revisions that were required.

A March 13, 1990 meeting was held with LaSalle Laboratories and general discussion ensued.

A letter to Schering Corporation of August 17, 1990 stated the NDA was not approvable because of the deficiencies in the clinical, bioavailability and bioequivalence, biopharmaceutics, and labeling sections of the NDA. **(Attachment 3)**

A letter dated October 30, 1990 to Dr. James Simon at Georgetown University listed five comments/recommendation to improve his drug testing procedures. Classification: VAI-2 [Voluntary Action Indicated-level 2 (moderate problems)].

On July 2, 1990 representatives from LaSalle Laboratories and Schering Plough Corporation met with the FDA. The following studies were proposed by the FDA as "necessary (this medical reviewer's emphasis) for approval of Utrogestan. 1) A **good** study (perhaps at the 300 mg dose) that clearly shows secretory changes. It is possible that a dose greater than 300 mg may be needed. (A consultant stated that special estrogenic priming would be needed.) 2) Inter-subject variability is a problem with this drug; thus, a dose ranging study would be useful (e.g., 200, 300, 400 mg/day, possibly in divided doses). Endpoints should be classic Noyes-Hertig endometrial changes. It would not be necessary to show 100% secretory change; however, the drug should be compared to a normal endometrium or to treatment with another product. (Discussion of an appropriate active control raised questions regarding potential estrogenic activity in some progestins or the production of undesirable dose-dependent side effects.) 3) A bioavailability study might be desirable." Finally, the FDA clarified that the sponsor would have to show secretory changes in estrogen-primed endometrium and it would not have to be in post-menopausal women. Three cycles of treatment would be long enough if the endometrial changes could be demonstrated in that time.

The FDA met with Schering on July 23, 1991 to discuss the agency's not approvable letter of August 17, 1990. Schering proposed two studies (both in healthy males) to address the clinical pharmacology deficiencies, and one study to address the clinical deficiencies as noted in their July 11, 1991 submission. With the exception of using a classification of "marginal secretory activity", the proposed clinical study seemed adequate to the FDA.

A September 23, 1991 letter to Schering-Plough Corporation clarified two errors in their minutes in regard to the Pharmacology information of the July 23, 1991 meeting.

Description of Clinical Data

The clinical section of this application includes two randomized double-blind clinical trials. The first trial (#020 or T91-006) studied the safety and efficacy of 200 mg and 300 mg Prometrium vs. placebo in producing withdrawal bleeding in subjects with secondary amenorrhea. The second trial (C90-557) studied the efficacy and safety of 100, 200, 300, and 400 mg/day Prometrium vs. placebo (unopposed estrogen) in transforming proliferative to secretory endometrium in postmenopausal subjects who had been estrogen primed.

Clinical Studies

Indication: Treatment of secondary amenorrhea

Trial #1
The first Phase III study (Study No. 020 also called T91-006) was entitled "Double-blind evaluation of micronized progesterone (Utrogestan) and placebo in induction of withdrawal bleeding in patients with secondary amenorrhea". The primary investigator was James A. Simon, M.D., and was conducted in the Department of Obstetrics and Gynecology at Georgetown University Medical Center. The study resulted in a publication by Shangold MM, et. al entitled "Factors associated with withdrawal bleeding after administration of oral micronized progesterone in women with secondary amenorrhea" in *Fertility and Sterility* **56(6)**:1040, 1991 **(Attachment 4)**.

This study was previously reviewed by Medical Officer Ridgley Bennett in his review dated January 18, 1990. The following is a brief summary of the trial and its findings.

Design: Trial #1
This was a single-center, double-blind, parallel-group, placebo-controlled study in which patients with secondary amenorrhea were randomized to one of three treatment groups. The primary objective was to compare the efficacy and safety of micronized progesterone (Utrogestan) 200 mg and 300 mg with placebo in the initiation of withdrawal bleeding in patients with secondary amenorrhea. Subjects were to take the medication once daily at bedtime for 10 days.

Eligible subjects were normal healthy non-menopausal women over the age of 18 y.o. with secondary amenorrhea of at least 90 days duration, and the following baseline hormone values: FSH≤40 mIu/mL, LH≤40 MIu/mL, estradiol ≥60 pg/mL, progesterone ≤1 ng/mL, undetectable βHCG, DHEA-S ≤5000 ng/mL, and testosterone ≤200 ng/dL.

Sixty four women were randomized to one of three treatment groups. Two patients were eliminated for safety reasons, and two patients were randomized but did not receive treatment. The remaining 60 subjects (ages 17-48 y.o.) were randomized as follows: 200 mg (N=19), 300 mg (N=20), and placebo (N=21). The treatment period was 10 days.

Results Trial #1
The criteria used by the applicant for efficacy was any bleeding that occurred during the 10 days of treatment and the next 7 days

after the last day of treatment. Their analysis showed the following rates of bleeding:

300 mg	90% (18/20)
200 mg	53% (10/19)
placebo	24% (5/21).

A more common definition of withdrawal bleeding (and that utilized by the primary Medical Officer during the initial review) would be any bleeding that occurred after the last day of treatment but during the seven subsequent days. Using this definition the rates of bleeding would be the following:

300 mg	80% (16/20)
200 mg	37% (7/19)
placebo	10% (2/21).

Using either definition, the rate of bleeding in the 300 mg group was significantly different from the placebo group, while the 200 mg group was not significantly different.

The numbers of patients reporting treatment-emergent adverse events (regardless of relationship to treatment) were as follows:

300 mg group	71%(15/21)
200 mg group	80%(16/20)
placebo group	67%(14/21).

Most of the adverse events were classified as mild or moderate in severity. Severe adverse events were reported by 25%, 33%, and 19% of the subjects in the 200 mg Prometrium, 300 mg Prometrium, and placebo groups, respectively. The most commonly reported severe adverse event was abdominal pain (cramps) reported in 20%, 14%, and 10% of the subjects in each of the respective treatment groups. With the exception of somnolence reported in 10% of the subjects in the 300 mg dose group, all other severe adverse events were reported by only 1 subject.

None of the subjects in any of the three treatment groups discontinued treatment because of adverse events, and there were no deaths.

Reviewer's Comments/Conclusions Trial #1

Prometrium 300 mg/day, but not 200 mg/day, produced a significantly greater rate of withdrawal bleeding than did placebo. Using the usual definition of withdrawal bleeding (ie. that bleeding which starts after the last day of medication) the 300 mg dose of Prometrium produced an 80% withdrawal bleeding

rate. In the absence of either a literature reference to support the 80% efficacy rate, or an active control in the study design that would provide a comparator, this study does not provide information about the efficacy of Prometrium in relation to other approved therapy.

Trial #2

The second Phase III study (C90-557) was entitled "A three-cycle, double-blind, dose response efficacy and safety study of the endometrial histologic effects of oral micronized progesterone (SCH 961) compared to placebo in estrogen primed postmenopausal women". There were 10 centers in the United States that enrolled patients.

The objective of this study was to determine the endometrial progestational activity (as determined by light microscopy) of Prometrium (100 mg/day, 200 mg/day, 300 mg/day or 400 mg/day) compared to placebo (unopposed estrogen). Treatment would consist of Prometrium administered once daily with the evening meal for 10 days/cycle (days 16-25) concurrently with Premarin® (0.625 mg/day) administered daily in the morning (days 1-25) for three calendar month cycles. The subjects would be postmenopausal women who had been previously estrogen primed.

Design Trial #2

The study design had four phases. First, there was a one to four week screening phase. Second, a six week estrogen priming phase of Premarin® 0.625 mg/day was given in the morning for approximately six weeks (cycle #1 and days 1-15 of cycle #2). Near the end of this phase subjects had their baseline evaluations and endometrial biopsy. Third, was a three cycle randomized, double-blind treatment phase. Patients were randomized to one of the four doses of Prometrium or placebo. Biopsies were performed the morning after the last dose of treatment (day 26 of cycle #4). Fourth, was a follow-up phase when patients received Provera® 10 mg/day orally for 14 days. No specific time of day or relationship to meals was required for Provera® administration, consistent with product labeling. **Attachment 5** is a table of the study flow chart. As part of the study design a separate group of untreated premenopausal women underwent identical endometrial histological evaluation during days 8, 9, or 10 of the luteal phase of the menstrual cycle as a histologic "reference" group.

Medical reviewer's comment: The fourth phase of the protocol is somewhat unusual. It appears to use

Provera® to eliminate any residual hyperplasia left after treatment with Prometrium if the Prometrium proved to be ineffective.

Subjects eligible for estrogen priming had normal routine laboratory results, estradiol <25 pg/ml, FSH >40 mIU/ml, normal pap smears, and normal mammograms. The patients who completed estrogen priming were eligible for randomization to the double-blind treatment if their endometrial biopsy indicated a proliferative endometrium.

Of the 187 subjects enrolled, 152 entered in the estrogen priming phase, and 128 subjects were randomized to receive double-blind treatment. The safety [intent-to-treat(ITT)] population consisted of 124 subjects who received at least one dose of double-blind treatment (placebo N=24, 100 mg/day N=26, 200 mg/day N=26, 300 mg/day N=25, and 400 mg/day N=25).

Medical reviewer's comment: There is a substantial decrease in the number of subjects between enrollment to estrogen priming and between estrogen priming to randomization. No written explanation is provided by the sponsor.

Dose (mg)	Enrolled	E_2 Priming	Randomized	Safety/ITT	Efficacy	Dropout
0				24	23	1
100				26	22	2
200				26	21	4
300				23	19	4
400				25	22	2
Total	187	152	128	124	107	13

The efficacy-evaluable population consisted of 107 subjects [107/128 (84%)] who had completed all three cycles of double-blind treatment and had evaluable endometrial biopsies (placebo N=23, 100 mg/day N=22, 200 mg/day N=21, 300 mg/day N=19; and 400 mg/day N=22). The official requirements for a subject to be in the efficacy population were as follows: a) Subjects were to

have received at least 80% of the protocol-specified Premarin doses in each of cycles 1-4, and at least 80% of the protocol-specified double-blind medication in each of cycles 2-4; b) Subjects with an unreadable baseline (visit B1) biopsy were to be excluded from the efficacy population; and c) The visit B3 biopsy was to be performed the morning after the last dose of double-blind medication. The protocol specified visit B3 biopsy window was days 24-28 of cycle 4.
Prior to breaking of the blind, the following additional criteria were used to determine the efficacy population: 1) Subjects with a baseline (visit B1) serum progesterone level greater than 3x the upper limit of the normal follicular range (upper limit of normal = 50 ng/dl), or subjects receiving placebo with an end of double-blind treatment (visit B3) serum progesterone level treater than 3x the upper limit of the normal follicular range, were to be ~~ex~~cluded from the effi~~ca~~cy population; and 2) All subjects with an evaluable visit B3 biopsy were included in the efficacy population regardless of the interval between the last dose of double-blind medication and the visit B3 biopsy, provided that other validity criteria were met.

Of the 17 subjects eliminated from the ITT population, thirteen women (1 placebo, 2 Prometrium 100 mg, 4 Prometrium 200 mg, 4 Prometrium 300 mg, 2 Prometrium 400 mg) failed to complete the study. The primary reason for discontinuing treatment was the occurrence of adverse experiences (1 Prometrium 200 mg, 2 Prometrium 300 mg, 2 Prometrium 400 mg). One of the 400 mg Prometrium subjects discontinued due to dysmenorrhea and irritability. The remaining 4 Prometrium subjects discontinued due to mild to severe dizziness.
During analysis of the study results, similar efficacy analyses were obtained in an analyses in which the 17 excluded patients were assumed to have no secretory activity. A worst case analysis also yielded similar results as only 1 placebo patient was excluded from the sponsor's efficacy population.

The primary efficacy parameter was the histologic assessment of secretory endometrium following double-blind treatment by three independent pathologists using the Noyes criteria **(Attachment 6)**. Overall assessment of secretory activity was determined by the concurrence of two of the pathologists. A third pathologist evaluated biopsy specimens, the discordant specimens of the first two pathologists plus a random sample of concordant specimens, without knowledge of the evaluations of the other two pathologists.
A secondary efficacy parameter was the incidence of withdrawal bleeding. The relationship between serum progesterone concentration and secretory endometrium was also evaluated.

Results Trial #2

There was a high degree of agreement among the three pathologists in the postmenopausal biopsy readings (Kappa coefficient = 0.82). Efficacy results (endometrial secretory transformation in the efficacy population at the end of double-blind treatment compared to placebo) as calculated by the sponsor are as follows:

Dose	Total Secretory Activity	
placebo	0/23 (0%)	
100 mg/day	2/22 (9%)	p=0.23
200 mg/day	5/21 (24%)	p=0.02
300 mg/day	10/19 (53%)	p<0.001
400 mg/day	14/22 (64%)	p<0.001

The number of subjects with total secretory activity was defined as the sum of patients with partial or complete secretory activity, and the p values are calculated using Fisher's exact tests comparing to placebo. The sponsor concluded the following: 1)a dose- response relationship with respect to endometrial secretory transformation was established; 2) 200, 300, and 400 mg/day are significantly more effective than placebo (unopposed estrogen) in inducing endometrial secretory transformation, and 3) 300 and 400 mg/day were the most effective doses.

Medical reviewer's comment: The definition of "total secretory activity" is unusual and not a generally accepted endpoint for progestational activity. It is similar to the classification of "marginal secretory activity" objected to by the FDA in the July 23, 1991 meeting with Schering.

If the histological results of the endometrial biopsies are further stratified, different conclusions may be drawn (p values in the following table were determined by FDA Statistician Dan Marticello).

Treatment group	Secretory Activity					
	None	Partial	Complete N	Complete p value	Total N	Total p value
Placebo (unopposed E)	23	0	0	p=1	0	p=1
Prometrium 100 mg/day	20	2	0	p=1	2	p=.47
Prometrium 200 mg/day	16	5	0	p=1	5	p=.04
Prometrium 300 mg/day	9	7	3	p=.17	10	p<.001
Prometrium 400 mg/day	8	4	10	p<.001	14	p<.0001

This table supports the sponsor's conclusion that both Prometrium 300 mg/day and 400 mg/day had a significantly greater proportion of total secretory activity than did the corresponding placebo treatment. However, only Prometrium 400 mg/day had a significantly greater proportion ($p<0.001$) of complete secretory activity than did placebo patients.

Of the 17 subjects eliminated from the ITT population, 15 were excluded because a cycle 4 biopsy was not performed (1 placebo, 4 Prometrium 100 mg, 5 Prometrium 200 mg, 4 Prometrium 300 mg, and 3 Prometrium 400 mg). One of the Prometrium 100 mg subjects did have a cycle 4 biopsy (no secretory activity) but not within the specified 24 hours after the last double-blind treatment dose. One of the Prometrium 400 mg subjects also had a cycle 4 biopsy (no secretory activity) but was excluded because she did not have a baseline (cycle 2) biopsy performed.

Analysis of withdrawal bleeding data showed a dose-response effect with the highest rate of bleeding in the 400 mg/day group. The mean times to withdrawal bleeding calculated from the double-blind treatment ranged from 0 to 3 days. Apparently all cycles had similar results, but only data from cycle 3 was summarized since it was the only cycle without confounding factors such as biopsy procedures.

Number(%) of Subjects in the Efficacy Population with Withdrawal Bleeding After the Last Dose of Double-Blind Medication

Cycle	Placebo	100 mg/day	200 mg/day	300 mg/day	400 mg/day
#3	2/23(9%)	12/22(55%)	17/21(81%)	14/19(74%)	20/22(91%)

Predictors of secretory transformation. Blood samples were collected the morning after the last dose of double-blind therapy near the time of biopsy sampling for determination of serum progesterone level. Analysis of serum progesterone concentration-response relationships showed that higher concentrations of serum progesterone were strongly associated with a higher probability of endometrial secretory transformation. Three subjects from the efficacy population were not included in the following table because their serum progesterone data was missing.

Serum Progesterone Concentration-Response Relationships in the Efficacy Population at the End of Double-Blind Treatment (Visit

B3):

Serum Progesterone Concentration (ng/ml)	Total Secretory Transformation Response
≥1500	8/8(100%)
≥300-1499	16/37(43%)
≥50-299	5/25(20%)
<50	0/34(0%)

Prometrium of **at least** 300 mg/day is generally required to produce serum progesterone concentrations associated with a greater then 50% probability of endometrial secretory transformation (partial or complete at the Visit B3 biopsy). The probability of endometrial secretory transformation was approximately 50% at a serum progesterone concentration of 634 ng/dl.

Prometrium Dose-Serum Progesterone Concentration Relationships in the Efficacy Population at the End of Double-Blind Treatment (Visit B3):

Dose	N	Serum Progesterone Concentration (ng/ml)	
mg/day		Mean	Range
0	23	7	
100	21	130	
200	21	426	
300	18	576	
400	21	1526	

Two other variables were selected by the logistic regression analysis as making an additional contribution to the prediction of secretory transformation, although to a lesser extent: log-transformed estradiol concentrations were positively correlated with secretory transformation (p=0.036); in contrast, smoking appeared to reduce the probability of an endometrial secretory transformation (p=0.005), although the number of smokers was small.

Safety Trial #2

The safety population included all randomized subjects who were exposed to at least one dose of double-blind medication. Analysis of the safety data shows that the most commonly occurring adverse event with Prometrium (all doses) vs. placebo was dizziness (16% vs. 4%). With the exception of dizziness at doses of 300 mg/day and 400 mg/day, the incidence of adverse events did not appear to be dose-related. Other treatment-emergent adverse events reported with Prometrium compared to placebo were breast pain (11% vs. 8%), headache (10% vs. 8%), abdominal pain (cramps) (10% vs.13%), and fatigue (9% vs. 4%). Generally, dizziness and fatigue occurred during the start of double-blind treatment. The other common adverse events occurred throughout the double-blind treatment period with no particular relationship to the initiation of double-blind drug. Most adverse events were mild to moderate in severity.

Adverse events led to discontinuation in five subjects (5%) treated with Prometrium. Dizziness of varying severity led to discontinuation in four of the five subjects. Dizziness is a recognized side effect with other progestin-estrogen combinations.

Among severe (Grade 3) adverse events, abdominal pain (cramps) was the most common, occurring in 1 subject (4%) at 200 mg/day, in 2 subjects (8%) at 400 mg/day, and in 2 placebo patients (8%). No life-threatening (Grade 4) adverse events were reported.

Prometrium appeared to have no clinically relevant effects on vital signs, body weight, or physical examination results. Similarly, no clinically relevant effects on laboratory parameters were observed with the possible exception of lipid chemistries. Significant changes in lipid parameters occurred in 3 subjects at 100 mg/day, 5 subjects at 200 mg/day, 4 subjects at 300 mg/day, 6 subjects at 400 mg/day, and in 5 subjects receiving placebo. A summary of the mean changes in the lipid profile is shown in **Attachment 7**. There were decreases in high density lipoprotein cholesterol, and increases in very low density lipoprotein cholesterol and triglycerides in the Prometrium groups compared to placebo. However, the significance of these changes in a short-term study is unknown, but unlikely to be clinically important.

One serious adverse event (angina) was reported in a patient with a history of angina in the 300 mg/day group. The angina was considered unrelated to study treatment by the investigator (she had a prior history of angina), and the subject completed the study. There were no deaths.

There were no breast or endometrial malignancies observed. However, one subject in the 300 mg/day group did have simple hyperplasia without atypia at the end of double-blind treatment. Following treatment with Provera® 10 mg/day x 14 days, a repeat endometrial biopsy in this subject showed proliferative endometrium.

Medical reviewer's comment: The one patient who had simple hyperplasia without atypia at the end of Prometrium treatment is notable. It is also significant that this same patient had proliferative endometrium after a 14 day course of Provera®. My conclusions regarding this subject are twofold. First, the subject probably has some endogenous condition placing ~~her~~ at increased ris~~k~~ for endometrial resistance to progestins, and second that Prometrium 400 mg/day x 10 days is probably similar to the effectiveness of Provera® 10 mg/day x 14 days since neither medication transformed her endometrium to a secretory pattern, and since the difference between simple hyperplasia without atypia and proliferative endometrium may be minimal.

Reviewer's Comments/Conclusions Trial #2

Of the four doses studied, only the 400 mg/day dose produced a significantly greater proportion ($p<0.001$) of complete secretory activity in the subjects than did placebo.

In addition, the 400 mg/day dose had the highest frequency of withdrawal bleeding (91% from the last day of medication), and was significantly different from the 300 mg/day rate ($p<.04$). The efficacy of withdrawal bleeding for the 300 mg/day dose was 74%, which is similar to the results of Trial #1 (80%).

Most of the adverse events with Prometrium were mild to moderate in severity. With the exception of dizziness at the 300 mg/day and 400 mg/day doses, the incidence of adverse events did not appear to be dose-related.

The main limitation of Trial #2 in relation to the proposed indication of NDA 19,781 is that the 400 mg dose which was the most effective for secretory transformation and withdrawal bleeding was not studied in Trial #1; and the relevance of such findings in postmenopausal subjects to secondary amenorrhea subjects is not known. A second problem is the split dosing with the Premarin® administered in the morning and Prometrium administered in the evening. Once marketed, patients may be more

likely to take their medication at the same time rather than two different times. Therefore, the relevance of the study design to the probable real world clinical use of Prometrium may be very different.

Overview of Efficacy--Comparative results between studies
Both studies were randomized, double-blind, parallel-group, placebo controlled evaluations of the progestational activity of micronized progesterone, Prometrium.

Study 020 studied two doses of Prometrium, 200 and 300 mg, in the targeted population of subjects with secondary amenorrhea. However, the efficacy rates of withdrawal bleeding were low (37% and 80%, respectively) with only the 300 mg group rate being superior to placebo, and the efficacy rates of endometrial secretory transformation were not determined.

Study C90-557 used 100 mg, 200 mg, and 300 mg doses of Prometrium, as well as a 400 mg dose in a postmenopausal population. The results were that the 400 mg dose, which was not used in Study 020, had the highest efficacy rates for both withdrawal bleeding and endometrial secretory transformation. The findings of Study C90-557 are limited because it was performed in estrogen primed postmenopausal women rather than in the targeted population of women with secondary amenorrhea.

Thus, the apparent most effective dose (400 mg) has not studied in the targeted population.

Overview of Safety
A total of 186 women in these two clinical trials were evaluated for safety (62 subjects in Study 020 and 124 subjects in Study C90-557). In addition, safety data was collected on 70 (49 male and 21 female) normal volunteers from five pharmacokinetic/bioavailability studies.

No patient discontinued treatment in Study 020. In Study C90-557, 90%(111/124) of subjects completed the study; 10%(13/124) of subjects discontinued treatment prematurely. Twelve of the 13 subjects received Prometrium; the remaining subject received placebo. Adverse events resulted in discontinuation in 5%(5/100) of subjects who received Prometrium (one subject received 200 mg/day, two subjects received 300 mg/day, and two subjects received 400 mg/day of Prometrium). No placebo patients discontinued treatment because of adverse events. The remaining eight subjects discontinued treatment for other reasons. No subjects in either Study 020 or Study C90-557 discontinued treatment following randomization because of laboratory

abnormalities.

In both clinical trials Prometrium was well tolerated (mild to moderate in severity).
In Study 020 the most common treatment-emergent adverse events reported in subjects receiving Prometrium (N=41) compared with placebo (N=21) were abdominal pain (cramps, 46% vs. 24%), dizziness (12% vs. 14%), somnolence (12% vs. 5%), and fatigue (10% vs. 10%).
In Study C90-557 the most common treatment-emergent adverse events reported by the Prometrium subjects (N=100) compared with placebo (N=24) were dizziness (16% vs. 4%), headache (10% vs.8%), breast pain (11% vs. 8%), abdominal pain (cramps, 10% vs. 13%), and fatigue (9% vs 4%).
With the exception of dizziness, which occurred with the greatest frequency at Prometrium doses of 300 mg/day and 400 mg/day, the incidence of adverse events did not appear to be dose-related.

There were few severe treatment-emergent adverse events and no life-threatening adverse events.
In Study 020, a total of 29% (12/41) of Prometrium subjects vs. 19% (4/21) of placebo-treated patients reported severe treatment-emergent adverse events. This difference in incidence was primarily because more abdominal pain (cramps) occurred in subjects receiving Prometrium [17%(7/41) vs. 10%(2/21)]. This is consistent with the known pharmacologic action of progesterone.
In Study C90-557, severe treatment-emergent adverse events were reported by 10%(10/100) of subjects receiving Prometrium compared to 13%(3/24) of subjects receiving placebo.

There were no serious adverse events reported in Study 020. In Study C90-557, one subject receiving 300 mg/day reported a serious adverse event. She was 66 y.o. and in 1987 was diagnosed with hypercholesterolemia and angina. Blinded study medication was initiated on 1-16-94. In February 1994 she was unable to complete a stress test and angioplasties were performed. She completed Study C90-557 on 3-25-94 as scheduled. The investigator considered the event unrelated to the blinded study medication and Premarin®.

No deaths or treatment-emergent malignancies were reported during Studies 020 or C90-557.

Adverse events reported in the medical literature and from foreign marketing experience were reviewed. The most important report in the literature is from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. This trial was a 3-year, multicenter, randomized, double-blind, placebo-controlled

trial sponsored by the National Institutes of Health. A total of 875 healthy postmenopausal women were included. The PEPI authors concluded that Prometrium appeared to preserve many of estrogen's favorable effects on cardiovascular risk factors, including HDL-C.

Prometrium as Utrogestan® was first marketed in 1980, and now is marketed in 26 countries worldwide. Besins Iscovesco, Inc has received 36 post-marketing adverse events involving 31 subjects through the end of 1995. Most of these events were consistent with those previously reported for oral progestins or were attributable to the underlying indication for Prometrium. One report of fetal death in France and one report of pulmonary embolism in Switzerland were considered to be serious: all other reports were considered to be non-serious.
Since May 1995, Prometrium has been marketed by Schering-Plough in Canada for postmenopausal hormone replacement therapy. Through December 1995, 34 adverse events have been reported by 21 subjects. One report of fetal death in Canada was considered to be serious; all other reports were considered to be non-serious.

Labeling Review
Deferred until an approvable application is submitted.

Conclusions

1) Higher concentrations of serum progesterone were strongly associated with a higher probability of endometrial secretory transformation. While Prometrium at doses of 300 mg/day or 400 mg/day induced a greater frequency of withdrawal bleeding than placebo, the 400 mg/day dose was the most effective (91%) in a post-menopausal population.

2) While both 300 mg/day and 400 mg/day produced a significantly greater proportion of total secretory activity than placebo (partial and complete), only the 400 mg/day dosage produced a significantly greater proportion of complete secretory activity than placebo.

3) The most effective dose of 400 mg/day has only been studied in estrogen primed postmenopausal women.

4) The safety data seem adequate to support the use of Prometrium.

5) Prometrium seems to be well tolerated at the doses studied.

Recommendations

1 This application is not approvable because the most effective dose of 400 mg/day (which produced the highest frequency of withdrawal bleeding after discontinuation of medication as well as the only dose with a significantly greater frequency of complete secretory conversion compared to placebo) was not studied in the targeted population for the proposed indication (ie., women of reproductive age with secondary amenorrhea).

The sponsor has analyzed data based on an unacceptable definition of secretory changes, which include both partial and complete transformation. Complete secretory conversion is the appropriate endpoint for several reasons. First, it is the common clinical definition of secretory transformation. Second, a response less than complete would imply either that an inadequate dose of Prometrium was used, or that Prometrium was an ineffective progestin. Third, an irregular pattern or distribution of secretory transformation would probably result in prolonged bleeding due to irregular endometrial shedding.

2) In order to determine the most effective dose in the targeted population, the sponsor should conduct a Phase III study comparing the 300 mg/day and 400 mg/day doses in reproductive age women with secondary amenorrhea to include efficacy parameters of bleeding frequency, endometrial histology, side effects, and safety.

3) We recommend that the Phase III study include a positive control arm such as medroxyprogesterone acetate 10 mg/day for 10 days as well as a placebo.

4) The sponsor should be advised to conduct PK studies with the 400 mg dose in the target population of reproductive age women.

/S/

Craig S. Cropp, M.D.
Medical Officer, DRUDP

Concur: Heidi Jolson M.D. 10/8/96

cc:IND/NDA Arch.
HFN-340
HFD-580 (IND/NDA#
HFD-580/LRarick/HJolson/CMoore/CCropp///wpfiles.19781.nda

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-781

Attachment 1

AUG 17 1990

Schering Corporation
Attention: Douglass Given, M.D., Ph.D.
Vice President, Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Given:

Reference is made to your new drug application dated September 30, 1987, and resubmitted on March 17, 1988*, under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the preparation Utrogestan (progesterone capsules).

We also acknowledge receipt of your amendments dated October 23 and December 9, 1987; March 15, 1988; May 24, July 17, August 4 and 22, September 5 and 21, 1989; and January 24, 19, and 30, February 7, 16, and 23, April 3 and 9, May 11, and June 5, 1990.

We have completed our review and find that the information presented is inadequate and that the application is not approvable. The deficiencies are as follows:

1. Under section 505(d) of the Act and Title 21 of the Code of Federal Regulations (CFR) section 314.125(b), you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Utrogestan will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   The application contained a single study by Dr. Simon in patients with secondary amenorrhea. Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg; Utrogestan 200 mg was not statistically significantly different from placebo.

   The single study by Dr. Vargyas regarding the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

   The submitted published articles by Lane *et al.* (*British Medical Journal*, Volume 287, October 29, 1983) and King and Whitehead (*Fertility and Sterility*, Volume 46, December 1986) do not provide substantial evidence of a good progestational response with a dose 300 mg/day micronized progesterone.

   The application does not, therefore, provide substantial evidence of the efficacy of Utrogestan as claimed in the labeling.

* March 17, 1988 should read March 17, 1989

2. The application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) because it fails to provide the following bioavailability and bioequivalence information:

a. Review of the calculated AUC values for the different pharmacokinetic studies indicates that different values were submitted in the original NDA submission dated September 30, 1987, as compared to the values given in the March 17, 1989, submission. For example, an $AUC_{(0-24)}$ value of 471.55 for patient in Study 1 was given in the September 30, 1987, submission (volume 3, page 713) in comparison to a value of 404.307 in the March 17, 1989, resubmission (page 143). Please explain the discrepancies in the calculated AUC values for the different studies and indicate which values are correct. If the conclusions of the different studies are based upon incorrectly calculated AUC values, then new data analyses using the correct values will be required.

b. In Studies 1 and 2, the study designs were less than ideal with respect to bioavailability/pharmacokinetic considerations. That is, on Day 5 (assuming steady state) a complete blood level profile was not characterized over the entire 24 hr dosing interval (i.e., samples were only collected up to 10 hr post-dosing). This approach limits the utility of the results for accurately assessing drug accumulation (i.e., using AUC) and the overall effect of food on progesterone's oral availability under chronic administration and analyzing the steady state dose proportionality for the package insert's proposed dosing regimen. You should address these concerns and provide justification and additional data analyses as appropriate (e.g., the degree of error that is imposed as a result of using truncated AUC values on Day 5, etc.) to help support the accuracy of the conclusions from these studies.

c. In Study 3, two consecutive doses each of oral Utrogestan (200 mg Q.D.) and a marketed intramuscular (IM) product (50 mg Q.D.) were given in which blood samples were collected from Day 1 to 72 hr post dose on Day 2. From this study, you attempt to assess the relative bioavailability of the proposed market capsule to a marketed intramuscular reference product using $AUC_{(0-72)}$ following the Day 2 dose (i.e., actually $AUC_{(24-96)}$ following the dose at time zero on Day 1). Because of the limitations of this approach, we believe that the determined results are probably less than accurate.

For example, inspection of the observed blood level results indicates (i) for neither of the two study treatments are progesterone levels back to baseline before the Day 2 dose and (ii) steady state is not achieved by Day 2 (especially for the intramuscular dose) for which Day 2 $AUC_{(0-24)}$ values could have been used if steady state had been achieved. Due to progesterone levels being carried over from the first dose on Day 1 and the continuing accumulation of progesterone on Day 2 (especially for the IM route), the net result is that the relative bioavailability calculations using only Day 2 $AUC_{(0-72)}$ values will be biased. Therefore, based upon the study design employed, it would be better to use AUC calculated from Day 1 plus Day 2 to infinity to arrive at a more accurate assessment of relative bioavailability. You should determine the elimination rate constants and half lives for progesterone for each product and then conduct the relative bioavailability data analysis accordingly.

d. The application has only used t-tests for statistical comparisons and should have used analysis of variance (ANOVA) in order to analyze different sources of variation. The use of only a t-test does not allow one to ascertain effects other than the treatment comparison. The ANOVAs should use the following statistical model: Response = Sequence, Subject(Sequence), Period, and Treatment. This should be provided for all studies wherever applicable and then the Two One Sided Test Procedure should be employed for the treatment comparisons (see *Journal of Pharmacokinetics and Biopharmaceutics*, vol 15, no.6, 1987, pp 657-680) as for the dose normalized values (e.g., AUC and C_{max}) for study 2.

e. For Studies 1 and 2, you should establish when steady state was achieved in these studies (e.g., statistical analysis using C_{min} values using the ANOVA and the Two One Sided t-test Procedure).

f. The submission (volume 3 of 5, page 384) states that, "The Utrogestan product tested in the pharmacokinetic studies submitted in the application has a formulation identical to the product proposed for marketing in the U.S." It is further indicated that, "The formulation submitted to the IND with the study protocol was not used. Prior to initiation of the pharmacokinetic studies, the formulation of the capsule shell was changed to remove the parabens." You should address the following issues:

(1) Was the capsule formulation used in each of the pivotal clinical safety and efficacy studies the exact same formulation as was used in the pharmacokinetic studies and which is to be marketed?

(2) You should provide a table that lists each pivotal clinical and pharmacokinetic study number, the formulation of the capsule tested in each study, the batch number, the size of the batch, information whether it was a pilot or production size batch and whether it was made on production size equipment plus information about the mean size and range of the drug particles per study batch.

g. Metabolism as well as protein binding data should be submitted. These data could be obtained from the literature.

h. In Study 2, the dose proportionality of progesterone was studied at 100, 200 (2 * 100 mg capsule) and 300 mg (3 * 100 mg capsules) under fasting conditions. Knowing the significant effect of enhanced oral availability of progesterone when given with food at the 200 mg dose, it is important to know the consequences of food on the dose proportionality of the 300 mg dose. You should address this point with respect to the conduct of the clinical safety and efficacy studies.

3. We remind you that the labeling must comply fully with 21 CFR 201.57. We also have the following comments regarding the labeling:

We are reserving further comment on the proposed label and labeling until the application is found adequate in other respects.

We also have the following additional comments regarding the biopharmaceutics section of the applications:

1. You should clearly indicate how you have measured drug concentrations that exceeded the highest concentration of the linear dynamic range of the assay's standard curve for the collected blood samples. (The procedure involved, such as dilution or linear interpolation, should be clarified and documented).

2. It would be helpful if you provided for each study, the plasma concentration versus time plots for each study subject (preferably comparative treatment plots on the same scale). The data points should be joined in the plots in order to get a better idea of the fluctuations or patterns in drug blood levels.

3. You should define the meaning of "s.d." or "cv"; e.g., on page 382 of vol. 1.3, the summary table lists the parameters as mean ± cv (coefficient of variation). Tables IV to VIII on pages 459 through 464 list the same parameters as mean ± s.d. (standard deviation).

4. For appropriate evaluation of the rupture test, the application should include the individual capsule rupture times. The data should be provided with the mean and coefficient of variation.

5. In Study 1 which evaluated the effect of food on Utrogestan absorption, it was shown that food increased the extent of progesterone's oral availability about two-fold based upon mean AUC values and increased peak drug concentrations about four-fold based upon mean peak concentrations. The application should indicate if, in the pivotal clinical safety and efficacy studies, patients were instructed to take Utrogestan with or without meals or whether they were uncontrolled as to when Utrogestan was given in relation to meals. Additionally, the application should

describe the dosing regimens with respect to meals in all of the pivotal clinical studies -- knowing that food appears to significantly affect the oral availability of progesterone.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment or follow one of the other options under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply (one which does not address all remaining outstanding deficiencies) will not be processed as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions regarding this NDA, please contact Ms. Enid Galliers at 301-443-3490.

Sincerely yours,

/S/ 8/16/90

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

8.1.90 sig

cc: NDA Arch.
HFD-510
HFD-500/LRipper
HFD-80
HFD-510/RBennett/KRaheja/HNunn
HFD-426/JHunt
HFD-713/DMarticello
HFD-510/EGalliers/7.16,17,18,19.90/8.1.90/ft/8.1.90/ \19781na2.nda
Concurrences:REastep/DHertig/AJordan/HNunn/7/18/YChiu/7/19/RBennet/7/20/90/
PCorfman/7/20/PSathe/JHunt/8/1/90/

NOT APPROVABLE

Attachment 2 1

Complete Response to August 17, 1990 Non-Approval Letter

Comment 1

Under section 505(d) of the Act and Title 21 of the Code of Federal Regulations (CFR) section 314.125(b), you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Utrogestan will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

The application contained a single study by Dr. Simon in patients with secondary amenorrhea. Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg; Utrogestan 200 mg was not statistically significantly different from placebo.

The single study by Dr. Vargyas regarding the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

The submitted published articles by Lane et al. (British Medical Journal, Volume 287, October 29, 1983) and King and Whitehead (Fertility and Sterility, Volume 46, December 1986) do not provide substantial evidence of a good progestational response with a dose 300 mg/day micronized progesterone.

The application does not, therefore, provide substantial evidence of the efficacy of Utrogestan as claimed in the labeling.

Response to Comment 1

In this NDA Amendment, we are submitting information demonstrating the efficacy of micronized progesterone based on two well controlled clinical trials:

- Study 02,(T91-006) a single center trial conducted by James Simon, M.D. and sponsored by La Salle Laboratories.
- Study C90-557, a multi-center study sponsored by Schering Corporation.

Progestational activity of micronized progesterone was evaluated in the single-center clinical study (Study 02). Efficacy and safety of micronized progesterone 200 mg and

300 mg was compared with placebo in the initiation of withdrawal bleeding in premenopausal women with secondary amenorrhea. Results of this study indicated that micronized progesterone administered at a dose of 300mg/day was significantly more effective than placebo in the induction of withdrawal bleeding[a]. A 90% response rate (regardless to whether or not they bled prior to the end of treatment) was observed in the target population at this dose. As this study was submitted to the Agency on March 17, 1989 and resubmitted as an amended report on May 24, 1989 by La Salle Laboratories, it is not replicated in this Amendment; however, a synopsis of this study and the publication are included in **Section 8.D. Controlled Clinical Studies**

Since Study 02 only evaluated the clinical endpoint of withdrawal bleeding, and did not examine the histologic effects of micronized progesterone on the endometrium, the FDA requested that Schering Corporation characterize the secretory activity of micronized progesterone in support of Study 02.

Based on discussions between the FDA and Schering Corporation[b], a second study (C90-557) was designed to determine whether SCH 961 can effectively induce endometrial secretory transformation, assessed by endometrial biopsy, in postmenopausal women with a proliferative endometrium induced by estrogen priming (this patient model was reported commonly in the literature). In this multi-center, double-blind study, 100 mg, 200 mg, 300 mg, or 400 mg of SCH 961 or placebo (unopposed estrogen) was administered cyclically (10 days per cycle) with the evening meal for three calendar month cycles. Premarin® (0.625 mg/day) was administered daily in the morning. In addition to the dose levels examined in Study 02 (200 mg/day and 300 mg/day), Study C90-557 incorporated one dose level below and above (100 mg/ day and 400 mg/day) those previously studied to further explore a dose-response relationship of progestational activity. This study demonstrated the ability of micronized progesterone to significantly transform a proliferative endometrium into a secretory endometrium as evidenced by light microscopic histologic evaluation at doses of 200 mg/day, 300 mg/day and 400 mg/day compared to placebo(unopposed estrogen). The final report for study C90-557 is included in **Section 8.D. Controlled Clinical Studies**

[a]Withdrawal bleeding incidences were the same whether withdrawal bleeding interval was defined as vaginal bleeding occurring from the beginning of drug therapy up to and including one week following the final dose: or from the termination of drug therapy(excluding those patients who bled prior to termination of drug) up to and including one week after the final dose; or from the termination of drug therapy(inclusive) up to and including one week following the final dose(regardless of whether the patient bled prior to the end of treatment)

[b]Discussions and correspondences referenced include those dated: July 23, 1991; August 16, 1991, October 15, 1992; November 4, 1992; December 22, 1992; February 22, 1993; April 7, 1993; April 23, 1993; June 1, 1993, September 29, 1993 and March 2, 1995

It should be noted that Schering Corporation is not utilizing the data from the single-center study conducted by Dr. Joyce Vargyas, for which the medical report was submitted to IND to support the claimed indication of secondary amenorrhea.

This study evaluated the prevention of endometrial hyperplasia in postmenopausal women who received a 200 mg/day dose of micronized progesterone (a dose not currently considered efficacious for secondary amenorrhea) with estrogen. However, since patients were exposed to micronized progesterone, safety data from the Vargyas study is included in a synopsis in **Section 8.F., Other Studies and Information** and summarized

In 1990, it may have been believed that the published references by Lane et al. (British Medical Journal, Volume 287, October 29, 1983) and King and Whitehead (Fertility and Sterility, Volume 46, December 1986) did not provide substantial evidence that 300 mg micronized progesterone demonstrated a good progestational response in estrogen primed postmenopausal women. Comparison is limited between different progestational agents studied in a similar manner since different estrogen doses were used, ie 0.625 mg conjugated estrogens with other progestins vs 1.25 mg conjugated estrogens with micronized progesterone. Since progestational effects are dependent on the estrogenic environment, it is difficult to compare the progestational activity of progesterone to other agents studied that were slightly different. It is also difficult to predict from these evaluations the incidence of secretory transformation in premenopausal women with secondary amenorrhea. However the literature reported that a dose of 300 mg/day micronized progesterone achieved responses, ie secretory transformation, approaching the physiological range and that doses greater than 300 mg may be required to increase the effectiveness of the response.

Since these publications alone did not provide sufficient information for the claimed indication, Schering conducted a study (C90-557) which was designed to complement Study 02 (induction of withdrawal bleeding evaluated in premenopausal women with secondary amenorrhea) using a similar experimental model used by Lane et al and King and Whitehead(estrogen-primed postmenopausal women evaluated for endometrial light microscopic histologic characterization of secretory changes).

The results of the C90-557 study provide support of the micronized progesterone's mechanism of action (secretory transformation) at doses of 300 mg/day and 400 mg/day micronized progesterone.

Comment 2(a, b, c, d, e, and h) and Biopharmaceutic Comments 1, 2, 3 and 5

The application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) because it fails to provide the following bioavailability and bioequivalence information: (Please note these comments are paraphrased and summarized from the August 17, 1990 non-approval letter since they were previously responded to on December 5, 1990)

- The study design of two of the three Besins studies (Study 1 and Study 2) were less than ideal with respect to bioavailability and pharmacokinetic considerations due to serum samples not collected over the entire 24hr post dose period which limited adequate characterization of the drug's pharmacokinetic profile related to the overall food effect, drug accumulation, and dose proportionality. Justification and appropriate additional data were requested to support the accuracy of the conclusions from these studies. (**Comment 2b**)

- Clarification and re-calculation of pharmacokinetic parameters, (ie, AUC and steady state) was requested for Besins studies (Study 1 and Study 2), inclusion of individual subject serum concentration versus time plots and mechanism used to measure drug concentrations that exceeded the highest concentration of the linear range of the standard curve. (**Comments 2a, 2e and Biopharmaceutics Comments 1, 2**)

- Address limitations related to the relative bioavailability based on the proposed market capsule to a marketed intramuscular reference product (Besins Study 3)(**Comment 2c**)

- Statistical comparisons using analysis of variance were requested, as well as clarification of the definitions of "s.d" or "c.v."(**Comment 2d and Biopharmaceutics Comments 4**)

- Address the food effect issue as it relates to the conduct of the clinical safety and efficacy studies. (**Comment 2h and Biopharmaceutics Comment 5**)

Response to Comment 2(a, b, c, d, e and h) and Biopharmaceutic Comments 1, 2, 3 and 5

Responses to the August 17, 1990 FDA Comments 2(a, b, c, d, e and h) and Biopharmaceutic Comments 1, 2, 3, and 5 were submitted in a December 5, 1990 response (see Attachment 2). This response included a proposal to conduct two pharmacokinetic(food effect and dose proportionality) studies to address the deficiencies identified in the Besins studies. Subsequent to the response submitted in December 1990, revised study designs to evaluate the food effect and dose proportionality were proposed by Schering and accepted by the FDA at a July 23, 1991 meeting. The changes in the study designs were aimed at:
a) obtaining food effect and dose proportionality data at the projected clinical dose of 300 mg/day in subjects that reflected the age of the target population; b) reducing the variability in progesterone pharmacokinetics by standardizing the time of dosing relative to the time of day, meals, and diurnal activity; and
c) the use of males, a more homogeneous population with very low endogenous progesterone concentrations, to replace females as the study population to minimize the intra- and inter-subject variability in progesterone pharmacokinetics.

The two pharmacokinetic studies that were conducted by Schering Corporation are:

C91-255-01	SCH 961: A Study Evaluating the Effect of Food on the Oral Bioavailability of Prometrium®: A Four-Way Crossover Study in Normal Male Volunteers
C91-259-01	SCH 961: A Study Evaluating the Pharmacokinetic Profile and Dose Proportionality of Progesterone after Administration of Prometrium® Capsules: A Four-Way Crossover Study in Normal Male Volunteers.

The analytical and statistical methods used in these Schering conducted pharmacokinetic studies addressed concerns (ie, clarification of the procedure involved in assaying progesterone concentrations greater than the highest control sample of the standard curve, inclusion of individual serum concentration versus time plots and appropriate statistical comparisons) raised by FDA in August 1990 with respect to the studies conducted by Besins. These methods and results are described in detail in the individual study reports included in **Section 6.B. Human Pharmacokinetics and Bioavailability Study Reports** of this NDA Amendment and are summarized in **Section 6.A. Human Pharmacokinetics and Bioavailability** and **Section 8.C. Clinical Pharmacology** of this NDA Amendment.

The administration of oral micronized progesterone with food or in a post-prandial state up to four hours after a meal generally increases the bioavailability; however, this effect is quite unpredictable since it exhibits both high intra- and inter-subject variability(Study C 91-255). Serum progesterone concentrations appear linear and dose-proportional following multiple dose administration of micronized progesterone 100, 200, 300 and 400 mg/day(Study C91-259). Steady state serum concentrations were attained by Day 7, ie, following 6 consecutive daily doses of micronized progesterone, as determined by Cmin values. The serum elimination half-life of progesterone was determined to be independent of dose and ranged between 16 and 17 hours.

In the December 1990 response, Schering acknowledged that the study designs of the Besins Studies 1 and 2 were flawed due to an inappropriate blood sampling scheme (samples were not collected 10-24 hours post-dose). Specifically, these flaws impacted optimal characterization of the AUC, whereas the pharmacokinetic parameters such as Cmax and Tmax were considered to be adequately characterized. At that time, there was no other information available which could have supported the results of Besins Studies 1 and 2, thus Schering agreed that the Besin study sampling scheme did not provide for adequate characterization of the drug's pharmacokinetic profile over the entire 24 hour dosing interval and therefore conducted the pharmacokinetic studies described above. However, when the results of the recently conducted Schering pharmacokinetic studies are examined in conjunction with those from the Besins conducted studies, the results of the Schering conducted studies corroborate the findings of the Besins studies. While samples were not obtained 10-24 hours post dose to enable determination of the corresponding AUC values in Study 1 and 2, concentrations were found to be low 10-24 hours post dose in Study C91-259, and thus the contribution between 10-24 hours to the AUC is felt to be minimal. Despite the differences in the populations (the Besins Studies were conducted in post-menopausal women and the Schering Studies were conducted in healthy males) and the possible underestimation of AUC (0-24) in the Besins studies (due to the absence of blood collection between 10 to 24 hours post dose), there is generally good agreement across these two sets of studies in the progesterone pharmacokinetic parameters. Thus, the data from the Schering pharmacokinetic data supports the Besins generated pharmacokinetic results.

To address the concern on the food effect as it related to the conduct of the clinical efficacy and safety trial (C90-557), progesterone was administered with the evening meal to standardize the effect of food since Study C91-255 showed increased bioavailability with food or in a post-prandial state up to four hours. The choice of the evening was to maintain consistency in dosing times with the clinical Besins Study 02(dosing at bedtime).

Comment 2.f

The submission (volume 3 of 5, page 384) states that, "The Utrogestan product tested in the pharmacokinetic studies submitted in the application has a formulation identical to the product proposed for marketing in the U.S." It is further indicated that, "The formulation submitted to the IND with the study protocol was not used. Prior to initiation of the pharmacokinetic studies, the formulation of the capsule shell was changed to remove the parabens." You should address the following issues:

(1) Was the capsule formulation used in each of the pivotal clinical safety and efficacy studies the exact same formulation as was used in the pharmacokinetic studies and which is to be marketed?

(2) You should provide a table that lists each pivotal clinical and pharmacokinetic study number, the formulation of the capsule tested in each study, the batch number, the size of the batch, information whether it was a pilot or production size batch and whether it was made on production size equipment plus information about the mean size and range of the drug particles per study batch.

Response to Comment 2f

2f(1) Besins Pharmaceuticals, France, filed the original NDA for Utrogestan® 100 mg capsules in September 1987. Subsequently, ownership of the NDA was transferred to LaSalle Laboratories and then to Schering Corporation.

The basic formula of the drug product was originally developed by Besins Pharmaceuticals, France. Both NDA sponsors manufactured drug product at

The drug product formulation, i.e. the capsule contents, used by Besins, LaSalle and Schering Corporation are identical. This formulation has not changed for the entire product development and clinical program. The capsule shell formulas are qualitatively identical but differ slightly quantitatively with respect to gelatin and glycerin (see Table 1). This quantitative difference does not impact on capsule shell behavior or performance. The Schering formulation for both the capsule shell and its contents (designated as No. 2744) has not changed since its introduction in product development. The Schering formulation as defined in Table 1 will be the marketed formulation.

Table 1

Comparison of Besins and Schering Formulations

Ingredient	Amount per capsule (mg)	
	Besins Formula[a]	**Schering Formula [b] No. 2744**
Capsule Contents		
Progesterone USP Micronized		
Peanut Oil NF		
Lecithin NF		
Capsule Shell		
Gelatin NF		
Glycerin USP		
Titanium Dioxide USP		
FD&C Red No. 40		
D&C Yellow No. 10[d]		

[a]Besins formula used for Batch No. RPS E-13401
[b]Schering Corp. formula no. 2744 used for Batch Nos. RPS 22708, RPS 32578, RPS 38859 and RPS 46619
[c]Removed during drying
[d]The composition of the drug product submitted in the original NDA (Volume 1.1, pages 007 and 038) contained a typographical error in the amount of D&C Yellow No. 10. The correct amount of D&C Yellow No. 10 per capsule is mg.

2f(2) Table 2 summarizes the formulation, batch number, batch size, equipment scale used, date of manufacture, and drug substance lot number for the batches used in the pivotal clinical and pharmacokinetic studies as requested. All batches listed were manufactured at The pilot scale and production scale equipment used are of similar design and principle of operation, varying only in scale. Table 3 lists progesterone particle size data obtained by microscopy for the drug product batches listed in Table 2. This particle size method did not determine the mean size or range of the drug particles. Rather, the drug particle size was controlled by the percentage of particles below a target size. The particle size method was developed in 1987, prior to the submission of the original NDA, and used for all drug substance lots after that date. Retain samples of earlier drug substance lots were tested when available, otherwise drug product batches were tested. Since progesterone is poorly soluble in peanut oil, the particle size data from the suspended drug product can be readily compared to the data from the drug substance. The method was consistent throughout the product development. A sample of drug substance or drug product was evaluated with respect to three particle size specifications: μm. Drug substance lot no. 2082 and the corresponding product were unavailable for evaluation by this method.

The particle size data from Table 3 demonstrates that the four lots of progesterone drug substance for which data are available, i.e. lot nos. 2063, 2020, 961 and 3378, have similar populations when measured at μm. At μm, the populations range from a low of %(lot no. 2063) to a high of %(lot no. 2020). Drug product batches RPS 32578 (manufactured with drug substance lot no. 2020) and RPS E-13401 (manufactured with drug substance lot no. 2063) were used in the pharmacokinetic studies conducted by Schering Corporation and Besins, respectively. As reported in **Section 6A. Human Pharmacokinetics and Bioavailability** of this NDA Amendment, the pharmacokinetic results of these studies were found to be

generally in good agreement. Furthermore, drug substance batches 961 and 3378 used in the clinical study have particle size data within the range of the batches used in the pharmacokinetic studies.

In order to have a less subjective particle sizing test method, and to better define the particle size below μm, a new instrumental test method was developed. This method is referred to as the method ; **see Section 3.A.4. Drug Substance Specifications and Analytical Methods**: Specification Development Report for Progesterone, USP, micronized, for the justification of the current particle size specification.

Table 2

Summary of Data for Batches Used in Pharmacokinetic and Clinical Studies

Study No.	Formulation	Batch No.	Batch Size (capsules)	Equipment*	Date of Manufacture	Drug Substance Lot No.
PK Studies						
Study No. 1 Study No. 2 Study No. 3	Besins	RPS E-13401		Pilot Plant	11/06/85	2063
Study C91-255 Study C91-259	Schering	RPS 32578 (SP 25529-060)		Production	06/19/90	2020
Clinical Studies						
Simon Study 02 (T91-006)	Schering	RPS 22708		Pilot Plant	01/22/87	2082
Study C90-557	Schering	RPS 38859 (SP 28173-064)		Pilot Plant	03/02/92	961
	Schering	RPS 46619 (SP 30451-091)		Pilot Plant	10/12/93	3378

*Equipment used to manufacture the bulk suspension depends on batch size.
The encapsulation machine used in Production is identical to the one used in the Pilot Plant.

SP: Schering Corporation

Table 3

Particle Size Data for Progesterone Drug Substance Besins Microscopic Methodology

Drug Product Batch No	Drug Substance Lot No	Particle Size		
		<10 µm	<20 µm	<60 µm
RPS E-13401	2063	(84%)[a]	(98%)	(100%)
RPS 32578 (SP 25529-060)	2020	97% (94%)[a]	100% (99%)	100% (100%)
RPS 22708	2082	N/A	N/A	N/A
RPS 38859 (SP 28173-064)	961	91%	98%	99%
RPS 46619 (SP 30451-091)	3378	88%	97%	99%

[a]( ): Data obtained from Drug Product

N/A: Data not available

SP: Schering Corporation

APPEARS THIS WAY
ON ORIGINAL

Comment 2.g.

Metabolism as well as protein binding should be submitted. These data could be obtained from the literature.

Response to Comment 2.g.

Progesterone metabolism and protein binding data obtained from the literature were submitted on December 5, 1990. This information as well as additional information on metabolism and protein binding are included in **Section 5.C. Nonclinical Drug Metabolism Technical Summary** and in **Section 6.A. Human Pharmacokinetics and Bioavailability** of this NDA Amendment. The following conclusions presented in this NDA Amendment support those previously submitted:

- Progesterone is metabolized in all species by . Based on metabolic data in plasma, urine and hepatic microsomes, the disposition of progesterone in humans appears to be similar to that of cynomolgus monkeys.

- Progesterone is approximately bound 96-99% to serum proteins, primarily to albumin and transcortin.

Comment 3

We remind you that the labeling must comply fully with 21 CFR 201.57. We also have the following comments regarding the labeling:

Response to Comment 3

A revised package insert addressing all of the Agency's concerns is included in **Section 2.A. Proposed Drug Labeling** and in **Section 4.C. Labeling** of this NDA Amendment. The following are extracts from the package insert addressing each of the comments:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Biopharmaceutic Comment 4

For appropriate evaluation of the rupture test, the application should include the individual capsule rupture times. The data should be provided with the mean and coefficient of variation.

Response to Comment 4

LaSalle, a U.S. subsidiary of Besins-Iscovesco, the original sponsor of the NDA used a capsule rupture test which provided information similar to that of disintegration since a satisfactory dissolution procedure was not available. Schering Corporation has recently developed a dissolution procedure, which will replace the capsule rupture procedure. Further evaluation of the rupture test is no longer necessary since this test has been superseded by the dissolution test and is no longer in this NDA.

The dissolution procedure for micronized progesterone capsules utilizes the USP Apparatus 3 and a hydroalcoholic media. The proposed dissolution specification is C % dissolved in minutes. A detailed summary of the development of the dissolution procedure is in **Section 3.B.6. Drug Product: Specifications and Analytical Methods** and a summarization of dissolution information is in **Section 6.A. Human Pharmacokinetics and Bioavailability, Attachments E and F** of this NDA Amendment.

J:\LECHNER\PROMRESP

Attachment 3

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AUG 17 1990

NDA 19-781

Schering Corporation
Attention: Douglass Given, M.D., Ph.D.
Vice President, Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Given:

Reference is made to your new drug application dated September 30, 1987, and resubmitted on March 17, 1988, under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the preparation Utrogestan (progesterone capsules).

We also acknowledge receipt of your amendments dated October 23 and December 9, 1987; March 15, 1988; May 24, July 17, August 4 and 22, September 5 and 21, 1989; and January 24, 19, and 30, February 7, 16, and 23, April 3 and 9, May 11, and June 5, 1990.

We have completed our review and find that the information presented is inadequate and that the application is not approvable. The deficiencies are as follows:

1. Under section 505(d) of the Act and Title 21 of the Code of Federal Regulations (CFR) section 314.125(b), you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Utrogestan will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   The application contained a single study by Dr. Simon in patients with secondary amenorrhea. Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg; Utrogestan 200 mg was not statistically significantly different from placebo.

   The single study by Dr. Vargyas regarding the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

   The submitted published articles by Lane *et al.* (*British Medical Journal*, Volume 287, October 29, 1983) and King and Whitehead (*Fertility and Sterility*, Volume 46, December 1986) do not provide substantial evidence of a good progestational response with a dose 300 mg/day micronized progesterone.

   The application does not, therefore, provide substantial evidence of the efficacy of Utrogestan as claimed in the labeling.

2. The application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) because it fails to provide the following bioavailability and bioequivalence information:

a. Review of the calculated AUC values for the different pharmacokinetic studies indicates that different values were submitted in the original NDA submission dated September 30, 1987, as compared to the values given in the March 17, 1989, submission. For example, an $AUC_{(0-24)}$ value of 471.55 for patient in Study 1 was given in the September 30, 1987, submission (volume 3, page 713) in comparison to a value of 404.307 in the March 17, 1989, resubmission (page 143). Please explain the discrepancies in the calculated AUC values for the different studies and indicate which values are correct. If the conclusions of the different studies are based upon incorrectly calculated AUC values, then new data analyses using the correct values will be required.

b. In Studies 1 and 2, the study designs were less than ideal with respect to bioavailability/pharmacokinetic considerations. That is, on Day 5 (assuming steady state) a complete blood level profile was not characterized over the entire 24 hr dosing interval (i.e., samples were only collected up to 10 hr post-dosing). This approach limits the utility of the results for accurately assessing drug accumulation (i.e., using AUC) and the overall effect of food on progesterone's oral availability under chronic administration and analyzing the steady state dose proportionality for the package insert's proposed dosing regimen. You should address these concerns and provide justification and additional data analyses as appropriate (e.g., the degree of error that is imposed as a result of using truncated AUC values on Day 5, etc.) to help support the accuracy of the conclusions from these studies.

c. In Study 3, two consecutive doses each of oral Utrogestan (200 mg Q.D.) and a marketed intramuscular (IM) product (50 mg Q.D.) were given in which blood samples were collected from Day 1 to 72 hr post dose on Day 2. From this study, you attempt to assess the relative bioavailability of the proposed market capsule to a marketed intramuscular reference product using $AUC_{(0-72)}$ following the Day 2 dose (i.e., actually $AUC_{(24-96)}$ following the dose at time zero on Day 1). Because of the limitations of this approach, we believe that the determined results are probably less than accurate.

For example, inspection of the observed blood level results indicates (i) for neither of the two study treatments are progesterone levels back to baseline before the Day 2 dose and (ii) steady state is not achieved by Day 2 (especially for the intramuscular dose) for which Day 2 $AUC_{(0-24)}$ values could have been used if steady state had been achieved. Due to progesterone levels being carried over from the first dose on Day 1 and the continuing accumulation of progesterone on Day 2 (especially for the IM route), the net result is that the relative bioavailability calculations using only Day 2 $AUC_{(0-72)}$ values will be biased. Therefore, based upon the study design employed, it would be better to use AUC calculated from Day 1 plus Day 2 to infinity to arrive at a more accurate assessment of relative bioavailability. You should determine the elimination rate constants and half lives for progesterone for each product and then conduct the relative bioavailability data analysis accordingly.

d. The application has only used t-tests for statistical comparisons and should have used analysis of variance (ANOVA) in order to analyze different sources of variation. The use of only a t-test does not allow one to ascertain effects other than the treatment comparison. The ANOVAs should use the following statistical model: Response = Sequence, Subject(Sequence), Period, and Treatment. This should be provided for all studies wherever applicable and then the Two One Sided Test Procedure should be employed for the treatment comparisons (see *Journal of Pharmacokinetics and Biopharmaceutics*, vol 15, no.6, 1987, pp 657-680) as for the dose normalized values (e.g., AUC and C_{max}) for study 2.

e. For Studies 1 and 2, you should establish when steady state was achieved in these studies (e.g., statistical analysis using C_{min} values using the ANOVA and the Two One Sided t-test Procedure).

f. The submission (volume 3 of 5, page 384) states that, "The Utrogestan product tested in the pharmacokinetic studies submitted in the application has a formulation identical to the product proposed for marketing in the U.S." It is further indicated that, "The formulation submitted to the IND with the study protocol was not used. Prior to initiation of the pharmacokinetic studies, the formulation of the capsule shell was changed to remove the parabens." You should address the following issues:

(1) Was the capsule formulation used in each of the pivotal clinical safety and efficacy studies the exact same formulation as was used in the pharmacokinetic studies and which is to be marketed?

(2) You should provide a table that lists each pivotal clinical and pharmacokinetic study number, the formulation of the capsule tested in each study, the batch number, the size of the batch, information whether it was a pilot or production size batch and whether it was made on production size equipment plus information about the mean size and range of the drug particles per study batch.

g. Metabolism as well as protein binding data should be submitted. These data could be obtained from the literature.

h. In Study 2, the dose proportionality of progesterone was studied at 100, 200 (2 * 100 mg capsule) and 300 mg (3 * 100 mg capsules) under fasting conditions. Knowing the significant effect of enhanced oral availability of progesterone when given with food at the 200 mg dose, it is important to know the consequences of food on the dose proportionality of the 300 mg dose. You should address this point with respect to the conduct of the clinical safety and efficacy studies.

3. We remind you that the labeling must comply fully with 21 CFR 201.57. We also have the following comments regarding the labeling:

We are reserving further comment on the proposed label and labeling until the application is found adequate in other respects.

We also have the following additional comments regarding the biopharmaceutics section of the applications:

1. You should clearly indicate how you have measured drug concentrations that exceeded the highest concentration of the linear dynamic range of the assay's standard curve for the collected blood samples. (The procedure involved, such as dilution or linear interpolation, should be clarified and documented).

2. It would be helpful if you provided for each study, the plasma concentration versus time plots for each study subject (preferably comparative treatment plots on the same scale). The data points should be joined in the plots in order to get a better idea of the fluctuations or patterns in drug blood levels.

3. You should define the meaning of "s.d." or "cv"; e.g., on page 382 of vol. 1.3, the summary table lists the parameters as mean ± cv (coefficient of variation). Tables IV to VIII on pages 459 through 464 list the same parameters as mean ± s.d. (standard deviation).

4. For appropriate evaluation of the rupture test, the application should include the individual capsule rupture times. The data should be provided with the mean and coefficient of variation.

5. In Study 1 which evaluated the effect of food on Utrogestan absorption, it was shown that food increased the extent of progesterone's oral availability about two-fold based upon mean AUC values and increased peak drug concentrations about four-fold based upon mean peak concentrations. The application should indicate if, in the pivotal clinical safety and efficacy studies, patients were instructed to take Utrogestan with or without meals or whether they were uncontrolled as to when Utrogestan was given in relation to meals. Additionally, the application should

describe the dosing regimens with respect to meals in all of the pivotal clinical studies -- knowing that food appears to significantly affect the oral availability of progesterone.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment or follow one of the other options under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply (one which does not address all remaining outstanding deficiencies) will not be processed as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions regarding this NDA, please contact Ms. Enid Galliers at 301-443-3490.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

Attachment 4

FERTILITY AND STERILITY
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Factors associated with withdrawal bleeding after administration of oral micronized progesterone in women with secondary amenorrhea*†

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Objective: To compare two dosages of oral micronized progesterone (P) and placebo for withdrawal bleeding and side effects.

Design: Prospective, randomized, double-blind.

Setting: Academic institution.

Participants: Out of 190 screened with oligomenorrhea/amenorrhea, 60 who qualified completed the study.

Interventions: A 10-day course of (1) oral micronized P 300 mg, (2) oral micronized P 200 mg, or (3) placebo.

Main Outcome Measures: Withdrawal bleeding, side effects, and changes in lipids. Endogenous estradiol (E_2) concentrations at baseline and P concentrations during treatment were correlated with bleeding response.

Results: Withdrawal bleeding occurred in 90% of women taking 300 mg, 58% of women taking 200 mg, and 29% of women taking placebo ($P < 0.0002$ for 300 mg versus placebo). Side effects occurred similarly among the groups (P = not significant). Lipid concentrations were unchanged. Endogenous E_2 and treatment P concentrations were of limited predictive value for withdrawal bleeding.

Conclusions: Progesterone 300 mg induced significantly more withdrawal bleeding than placebo, with similar side effects. Bleeding response cannot be predicted reliably from E_2 and P concentrations. Fertil Steril 1991;56:1040–7

Medroxyprogesterone acetate (MPA) is a recognized treatment for anovulatory oligomenorrhea and amenorrhea, providing endometrial protection against chronic unopposed estrogen while inducing a controlled shedding of the endometrium. The only proven benefits of progestational therapy for nonpregnant women are endometrial protection and reduced blood loss, but many adverse side effects may result, including drowsiness, lethargy, increased appetite, weight gain, fluid retention, mastalgia, cramps, and hyperlipidemia. Many investigators have sought an ideal progestogen that would provide the beneficial effect to the endometrium without promoting any detrimental effects. To date, this ideal agent remains elusive.

Medroxyprogesterone acetate traditionally has been used to induce withdrawal bleeding in testing

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† Presented in part at the 46th Annual Meeting of The American Fertility Society, Washington, D.C., October 15 to 18, 1990.
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‖ Department of Obstetrics and Gynecology, Georgetown University School of Medicine.
¶ Maryland Medical Laboratory, Inc.

for and treating an estrogen-primed endometrium, usually by administering 10 mg/d for 5 to 10 days. This test should not be done unless pregnancy has been excluded. Although the potential teratogenic effects of synthetic progestogens have been disputed,[1,2] medical-legal considerations clearly prevent the routine use of these agents in this setting. Oral micronized progesterone (P) does not carry the potential teratogenic effect of synthetic agents and recently has become widely available outside the United States for use in a variety of indications.

Although progestogens and oral P may be used to induce withdrawal bleeding from an estrogen-primed endometrium, little is known about the minimum effective oral dose or serum level necessary to induce withdrawal bleeding. Similarly, little is known about the relationship between endogenous estrogen concentration and the likelihood of bleeding after progestogen administration.

The purpose of this investigation was to answer the following questions: (1) Will 200 mg or 300 mg of oral micronized P induce withdrawal bleeding from an estrogen-primed endometrium? (2) What serum level of P must be attained to induce withdrawal bleeding from an estrogen-primed endometrium? (3) How soon after initiating P therapy does withdrawal bleeding begin? (4) What endogenous level of estrogen is needed to have withdrawal bleeding after P administration? (5) How frequently are side effects reported in women taking oral micronized P? (6) What lipid changes, if any, result from a short course of oral micronized P?

MATERIALS AND METHODS

One hundred ninety women with oligomenorrhea or amenorrhea were screened, and 64 qualified for enrollment in the study. All subjects were 18 to 52 years of age and in good health. All had a history of oligomenorrhea, currently had amenorrhea of 50 to 300 days in duration, and were on no hormonal medication. For those who met the above criteria, a complete medical history was obtained and a physical examination performed. A Papanicolaou smear, serum human chorionic gonadotropin (β-hCG) and estradiol (E_2) concentrations, and urinary office pregnancy test were performed. If the pregnancy test was negative and the serum E_2 ("screening E_2") was >50 pg/mL, each subject was asked to return the next morning, in the fasted state, to have blood and urine obtained for the following tests: complete blood count (CBC), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, protein, albumin, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, follicle-stimulating hormone (FSH), luteinizing hormone (LH), E_2 ("baseline E_2"), prolactin (PRL), dehydroepiandrosterone sulfate (DHEAS), testosterone (T), P, thyroxine (T_4), triiodothyronine (T_3), T_3 resin uptake, thyroid-stimulating hormone (TSH), total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, and complete urinalysis. To qualify for the study, subjects had to satisfy the following inclusion criteria: serum FSH and LH concentrations < 40 mIU/mL, screening or baseline E_2 concentration at least 50 pg/mL, P concentration < 1 ng/mL, undetectable serum β-hCG level, serum DHEAS concentration < 5,000 ng/mL, and serum T concentration < 200 ng/dL. These criteria were chosen to maximize the number of participants expected to have withdrawal bleeding in response to an adequate P challenge. This protocol was approved by the Institutional Review Board of Georgetown University, and written informed consent was obtained from all participants before enrollment. All women were informed that they might experience dizziness, lethargy, drowsiness, increased appetite, weight gain, fluid retention, or breast soreness from taking the medication.

Subjects who satisfied all admission criteria were randomized, in a double-blind fashion, to one of three groups, for a 10-day course of Utrogestan (oral micronized P prepared by Lasalle Laboratories, Washington, D.C.) or placebo. Medications were administered as follows: Utrogestan 200 mg (two 100-mg capsules and 1 placebo capsule) at bedtime, Utrogestan 300 mg (three 100-mg capsules) at bedtime, and placebo (3 placebo capsules) at bedtime. All participants were asked to document any vaginal bleeding or staining on a special menstrual calendar and to record all symptoms and side effects experienced.

Each participant had a fasting blood sample drawn between days 7 and 10 of therapy for measurement of P, total and fractionated cholesterol, and triglycerides. All subjects returned for a final interview, 2 to 4 weeks after completing medication, at which time they were asked about bleeding and side effects, and their menstrual calendars were collected. At this time, each woman was treated and counseled about her diagnosis. Appropriate follow-up was arranged in all cases.

Withdrawal bleeding was defined as any bleeding or staining from the beginning of treatment up to

and including 1 week after the final dose. This time limit was chosen to include those who probably bled from P withdrawal and to exclude those who may have done so for other reasons. The onset of bleeding was determined by computing the number of days between the first dose of medication and the initiation of withdrawal bleeding. The maximum number of days considered to be a positive response was, therefore, 16 days.

Two of those who initially qualified for enrollment failed to satisfy all inclusion criteria, and another two who satisfied all inclusion criteria dropped out after enrollment but before completion of the study. Thus, 60 subjects completed the entire study and were included in the data analysis.

Laboratory Methods

The following tests were performed by commercial laboratories using traditional methodologies: CBC, AST, bilirubin, alkaline phosphatase, protein, albumin, BUN, creatinine, calcium, phosphorus, T_4, T_3, T_3 resin uptake, and urinalysis. Using radioimmunoassay (RIA), TSH, FSH, LH, PRL, DHEAS, and T were performed by a commercial laboratory. Serum E_2 concentrations were determined by a commercial laboratory using a coated tube RIA kit for E_2 (made by Diagnostic Products Corporation, Los Angeles, CA); the sensitivity of this assay was 10 pg/mL, and the interassay and intra-assay coefficients of variation (CVs) were <15% and <12%, respectively. Serum P concentrations were determined in one assay, using a coated tube RIA kit with ^{125}I P as the labeled tracer (Diagnostic Products Corp.); the sensitivity of this assay was 0.1 ng/mL, and the intra-assay CV was <10%.

Fractionated cholesterol measurements were determined on serum collected in the fasting state. All analyses were performed in one assay on the American Monitor Parallel (American Monitor Corp., Indianapolis, IN). The cholesterol and triglyceride reagents were from Catachem (Catachem, Inc., Port Chester, NY). Cholesterol standardization was against the College of American Pathologists Reference Material for Serum Cholesterol (College of American Pathologists, Skokie, IL). The total and HDL-cholesterol procedures used a coupled enzymatic reagent system involving cholesterol esterase, cholesterol oxidase, and peroxidase with a chromogen. Before analysis of HDL-cholesterol, interfering substances were selectively precipitated with 50,000 molecular weight-dextran sulfate – Mg^{++}. Triglycerides were determined using a coupled enzyme system comprised of lipase, glycerokinase, glycerol phosphate oxidase, and peroxidase with chromogen. The LDL- and very low-density lipoprotein-cholesterols were calculated from the Friedewall formula.[3] At a cholesterol mean of 230 mg/dL, the intra-assay CV was <0.3%. At a triglyceride mean of 162 mg/dL, the intra-assay CV was <1.55%.

Statistical Methods

The proportions of women experiencing withdrawal bleeding were compared for the three groups (200 mg, 300 mg, and placebo) by χ^2 analysis. Yates' continuity correction was applied to the analysis because a binomial distribution was used to approximate the normal distribution of the data. The mean onset of bleeding was compared for the three groups by ANOVA. When a significant difference was detected, Tukey/Kramer Honestly Significant Difference multiple comparison procedure was applied to each pair of comparisons. Mean P concentrations were compared for the three groups using one-factor ANOVA, and Tukey/Kramer HSD was then applied to each pair of comparisons. Mean P concentrations were compared between those who experienced withdrawal bleeding and those who did not, using unpaired, one-tailed and two-tailed *t*-tests. The proportion of bleeders above and below several chosen P concentrations was compared using χ^2 analysis. The correlation between P concentration and onset of withdrawal bleeding was tested by regression analysis. Mean screening and baseline E_2 concentrations were compared between those who experienced withdrawal bleeding and those who did not, using unpaired, one-tailed and two-tailed *t*-tests. The proportion of bleeders above and below several chosen baseline E_2 concentrations was compared using χ^2 analysis. The *t*-test comparison of baseline E_2 levels was repeated for the 300-mg group and for the 200-mg group to see if bleeders and nonbleeders differed at different P doses and to ensure that a significant difference, if present, would be detected. The correlation between baseline concentration and onset of withdrawal bleeding was tested by regression analysis. The proportions of women experiencing side effects were compared for the three groups (200 mg, 300 mg, and placebo) by χ^2 analysis. Mean P concentrations were compared between those who did and those who did not experience side effects using unpaired *t*-test. Risk of bleeding as a result of P concentration was estimated using a logistic regression model with baseline E_2 held constant as a continuous variable. Risk of bleeding as a result

of baseline E_2 concentration was estimated using a logistic regression model with P concentration held constant as a continuous variable. Concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides on days 7 to 10 of therapy were compared with baseline values within each treatment group using paired, two-sided *t*-tests. Changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides (from baseline values to those on days 7 to 10) were compared among the three treatment groups using ANOVA. Changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were related to P concentrations on days 7 to 10 using regression analysis.

RESULTS

Demographic data were similar for the three groups of women. Withdrawal bleeding occurred in 18 of the 20 (90%) women taking 300 mg/d, in 11 of the 19 (58%) women taking 200 mg/d, and in 6 of the 21 (29%) women taking placebo. By χ^2 analysis, $P < 0.001$ for this 2 × 3 table, but only the 300-mg group was significantly different from the placebo group ($P < 0.0002$ with the continuity correction). The 300-mg and 200-mg groups were marginally different from each other ($P = 0.054$ with the continuity correction). The 200-mg group was not significantly different from the placebo group.

Two women reported only spotting without any bleeding. One of these women was in the 200-mg group, and the other was in the placebo group, as shown in Table 1. Spotters and bleeders were combined for the results reported subsequently, and delayed bleeders were excluded from the analysis, unless indicated otherwise.

When the analysis included only those who bled by day 16 (as we defined withdrawal bleeding), the mean onset of bleeding occurred 10.7 ± 0.7 days (mean ± SEM) after initiating therapy in women taking 300 mg/d, 8.1 ± 1.0 days after initiating therapy in women taking 200 mg/d, and 10.8 ± 1.8 days after initiating therapy in women taking placebo. The differences between these groups were not statistically significant by ANOVA.

However, when this particular analysis was expanded to include all those who had bleeding within 30 days after initiating treatment, a significant difference was found between those taking 200 mg and those taking placebo by ANOVA. In this case, mean onset of bleeding occurred 10.7 ± 0.7 days (mean ± SEM) after initiating therapy in women taking 300 mg/d, 9.5 ± 1.3 days after initiating therapy in women taking 200 mg, and 15.0 ± 2.6 days after initiating therapy in women taking placebo. By Tukey/Kramer, $P = 0.04$ for the 200-mg group versus the placebo group, whereas the other two comparisons (i.e., the 300-mg group versus the placebo group and the 300-mg group versus the 200-mg group) did not differ significantly.

Table 1 Bleeding Response by Group

	300 mg	200 mg	Placebo
Bleeders	18	10	5
Spotters	0	1	1
Delayed bleeders[a]	0	2	3
Nonbleeders	2	6	12
Total	20	19	21

[a] Delayed bleeders had onset of bleeding > 16 days after initiating treatment.

Mean P concentrations were 12.4 ± 2.6, 4.4 ± 0.5, and 1.0 ± 0.4 ng/mL (mean ± SEM) for women taking 300 mg, 200 mg, and placebo, respectively. One-factor ANOVA showed $P < 0.0001$ for the three groups. By Tukey/Kramer, the comparisons between the 300-mg group and each of the other two groups showed $P < 0.05$, whereas the 200-mg group was not significantly different from the placebo group.

The mean P concentrations of withdrawal bleeders and nonbleeders are shown in Table 2, including means for the entire group and for each of the three groups alone. The proportion of bleeders was significantly greater for those who had P concentrations > 3.0 ng/mL compared with those who had P concentrations < 3.0 ng/mL ($P < 0.001$); the proportion of bleeders was significantly greater for those who had P concentrations > 2.5 ng/mL compared with those who had P concentrations < 2.5 ng/mL ($P < 0.01$); the proportion of bleeders was significantly greater for those who had P concentrations > 2.0 compared with those who had P concentrations < 2.0 ng/mL ($P < 0.01$). However, there was no P concentration above which women always bled and below which they never bled. There was no correlation between P concentration and onset of withdrawal bleeding (see Fig. 1).

The mean baseline E_2 concentrations of withdrawal bleeders and nonbleeders are shown in Table 2, including means for the entire group and for each of the three groups alone. When baseline E_2 levels of 30, 40, and 50 pg/mL were tested as cutoff points,

Table 2 Hormone Concentrations in Bleeders and Nonbleeders[a]

Group	P concentrations			Baseline E_2 concentrations		
	Bleeders	Nonbleeders	Probability	Bleeders	Nonbleeders	Probability
	ng/mL			pg/mL		
Entire	8.4 ± 1.7	2.6 ± 0.7	<0.01 (1-tailed) <0.02 (2-tailed)	99.8 ± 9.9	82.9 ± 8.5	NS[b]
300 mg	12.6 ± 2.9	10.1 ± 2.1	NS	113.5 ± 14.9	40.0 ± 20.0	0.064 (1-tailed) 0.128 (2-tailed)
200 mg	4.8 ± 0.7	3.2 ± 0.4	NS	75.5 ± 14.6	66.5 ± 14.1	NS
Placebo	1.8 ± 1.1	0.5 ± 0.1	NS	103.0 ± 22.8	87.1 ± 11.9	NS

[a] Values are means ± SEM.

[b] NS, not significant.

the proportion of bleeders above and below each value did not differ significantly (P = not significant [NS] for each tested cutoff point). There was no correlation between baseline E_2 concentration and onset of withdrawal bleeding (see Fig. 2). The results of the logistic regression analyses for P and baseline E_2 concentrations are shown in Tables 3 and 4.

When all symptoms were included in the analysis, side effects were reported by 15 of the 20 (75%) women taking 300 mg, by 15 of the 19 (79%) women taking 200 mg, and by 14 of the 21 (67%) women taking placebo (P = NS). When only symptoms associated with progestational therapy were included in the analysis, side effects were reported by 13 of the 20 (65%) women taking 300 mg, by 15 of the 19 (79%) women taking 200 mg, and by 13 of the 21 (62%) women taking placebo (P = NS).

When all symptoms were included in the analysis, the mean P concentration for those with side effects was 6.7 ± 1.3 ng/mL, and the mean P concentration for those without side effects was 4.8 ± 2.4 ng/mL (mean ± SEM) (P = NS). When only symptoms associated with progestational therapy were included in the analysis, the mean P concentration for those with side effects was 6.7 ± 1.4 ng/mL, and the mean P concentration for those without side effects was 5.1 ± 2.1 ng/mL (P = NS).

Baseline and treatment lipid values for the three groups are shown in Figure 3. There were no significant differences in total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides when treatment values were compared with baseline values (by t-test). The changes in total cholesterol were 3.8 ± 4.3 mg/dL for women taking 300 mg, −3.4 ± 3.8 mg/dL for women taking 200 mg, and 0.3 ± 4.8 mg/dL for women taking placebo (mean ± SEM). The changes in HDL-cholesterol were 0.8 ± 1.5 mg/dL for women taking 300 mg, −0.7 ± 2.0 mg/dL for women taking 200 mg, and −1.2 ± 2.7 mg/dL for women taking placebo (mean ± SEM). The changes in LDL-cholesterol were 2.6 ± 4.5 mg/dL for women taking 300 mg, −4.6 ± 4.0 mg/dL for

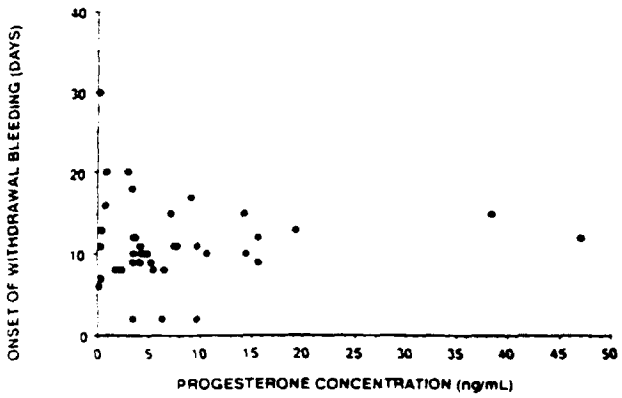

Figure 1 Onset of withdrawal bleeding versus P concentration.

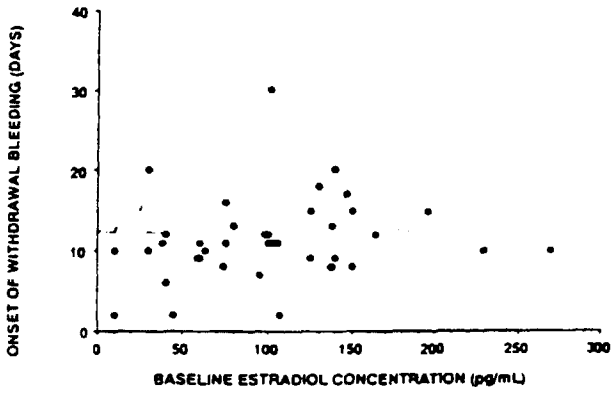

Figure 2 Onset of withdrawal bleeding versus baseline E_2 concentration.

Table 3 Odds Ratio for Bleeding Above P Concentration, Controlling for Baseline E_2 Concentration

P concentration	Odds ratio	95% CI[a]
ng/mL		
2.0	3.5 ± 0.38[b]	(1.66, 7.41)
2.5	2.7 ± 0.36[b]	(1.33, 5.51)
3.0	3.3 ± 0.36[b]	(1.64, 6.84)

[a] CI, confidence interval.
[b] Odds ratio is significant; values are ratio ± SE.

women taking 200 mg, and 1.3 ± 4.0 mg/dL for women taking placebo (mean ± SEM). The changes in triglycerides were 2.1 ± 6.9 mg/dL for women taking 300 mg, 9.1 ± 6.0 mg/dL for women taking 200 mg, and 1.3 ± 5.0 mg/dL for women taking placebo (mean ± SEM; P = NS for all of these comparisons). There was no correlation between changes in total or fractionated lipids and P level (by regression analysis).

DISCUSSION

We have previously shown that an endogenous serum E_2 concentration >40 pg/mL is of some value in predicting whether withdrawal bleeding will occur after a 5-day course of MPA (10 mg/d), and we have also demonstrated that no absolute concentration of E_2 will discriminate between those who have withdrawal bleeding and those who do not.[4] In the present investigation, we have confirmed our previous finding that no serum E_2 level can distinguish between bleeders and nonbleeders. Our previous finding that a serum E_2 level >40 pg/mL is of some value in predicting withdrawal bleeding was confirmed in the present study only when a logistic regression analysis was performed, holding the P concentration constant as a continuous variable. When this was done, odds ratios of 2.9, 1.9, and 1.3 were found for E_2 cutoffs of 30, 40, and 50 pg/mL, respectively. The lack of confirmation of our previous findings when only χ^2 analysis was employed may have been because of any of several factors: smaller numbers in the present investigation, varied P doses, and varied P concentrations. It is probable that, after an adequate P challenge, women with higher endogenous E_2 levels are more likely to have withdrawal bleeding, and larger numbers probably would have demonstrated this. However, it remains important that there is no endogenous level of E_2 above which women always bleed and below which they never bleed.

Kletzky et al.[5] have reported a mean E_2 concentration of 60 pg/mL in a group of 63 women who had withdrawal bleeding in response to either 100 mg or 200 mg of P in oil, intramuscularly (IM), and they reported a mean E_2 concentration of 18 pg/mL in a group of 27 women who had no withdrawal bleeding in response to either of these P dosages. Considerable overlap in the ranges of these two groups was noted, and this finding is consistent with our own observation. It is surprising that endogenous E_2 concentrations are not of greater predictive value when inducing withdrawal bleeding with a P challenge. This finding may be because of contributions to endometrial stimulation by estrone (E_1) and other estrogens, none of which were measured in this investigation. In subjects with chronic anovulation, follicular maturation is usually poor, and circulating concentrations of E_1 may exceed those of E_2.[6] Thus, total estrogens or estrogens other than E_2 may contribute more to endometrial stimulation than E_2 in such women.[6] Such estrogens undoubtedly affect bone density too and may, similarly, be at least as useful as E_2 in predicting bone loss or maintenance.

The range of P concentrations observed among women treated with a given dose of oral P probably reflects variations in absorption and metabolism. We have previously reported that concomitant food ingestion enhances the absorption of oral P.[7] In the present investigation, we asked our patients to eat and drink nothing after dinner (presumed to be approximately 6 to 7 P.M.) to perform lipid measurements on blood drawn after at least 12 hours in the fasting state. Because our subjects took their medication at bedtime, all P tablets were presumed to be taken without food. Blood samples were drawn approximately 10 hours after medication, at a time on the dose-response curve when little variation should occur.[7]

Table 4 Odds Ratio for Bleeding Above Baseline E_2 Concentration, Controlling for P Concentration

Baseline E_2 concentration	Odds ratio	95% CI
pg/mL		
30	2.9 ± 0.65[a]	(0.82, 10.61)
40	1.9 ± 0.48[a]	(0.76, 4.96)
50	1.3 ± 0.41[a]	(0.58, 2.90)

[a] Odds ratio is significant; values are ratio ± SE.

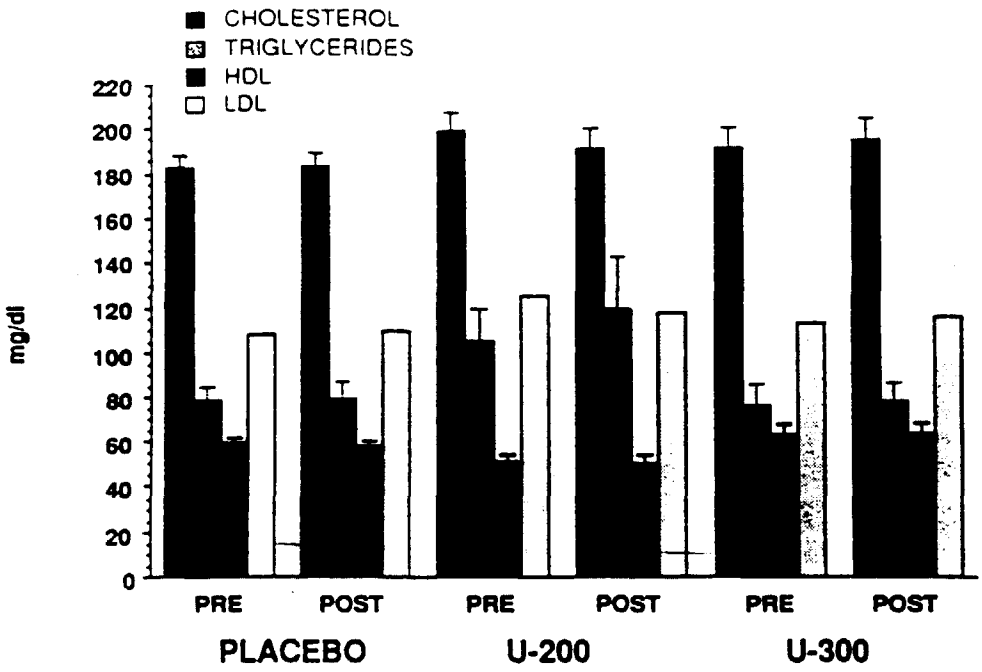

Figure 3 Concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides versus P dose before and during treatment (mean ± SEM).

Five subjects apparently ovulated spontaneously during the study: two who were taking 300 mg/d of oral P and three who were taking placebo. The two who probably ovulated at the beginning of medication (300 mg/d of P) had serum P concentrations of 38.5 and 47.1 ng/mL during treatment; their screening E_2 values were high, and their LH levels 1 to 2 days later (on the day they began medication) were high, suggesting a surge. The three who ovulated while taking placebo had serum P concentrations of 3.0, 2.3, and 7.1 ng/mL during treatment. All five subjects were included in the analysis of data. If others ovulated spontaneously during this study, we cannot detect this from our data.

It is surprising that side effects were equally frequent among the three groups in our study, particularly because P is generally associated with unpleasant side effects and would be expected to be more likely than a placebo to produce such side effects. The finding that 62% of women in the placebo group experienced progestational side effects is quite impressive and is undoubtedly related to the fact that they were informed at the time they entered the study that they might experience such side effects (required by Institutional Review Board). This serves to confirm the importance of placebo control in all studies.

The lack of effect on serum lipoproteins is important and has not been demonstrated previously. Ottosson et al.[3] have previously shown that oral micronized P 100 mg two times a day, when added to E_2 valerate 2 mg/d, led to no alteration in HDL-cholesterol. We have demonstrated that a 10-day course of oral P leads to no changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides, regardless of whether 300 mg/d or 200 mg/d is administered. This offers important advantages for postmenopausal women needing hormone replacement therapy, particularly because this group is at greater risk of cardiovascular disease than a younger group would be. However, it remains to be shown if long-term treatment will produce similar effects.

The safety of oral P for use during pregnancy offers additional advantages for use in premenopausal women: (1) this drug may be prescribed as a test of endometrial priming by estrogen without excluding pregnancy first; (2) this drug may be prescribed for endometrial protection on a regular basis in women presumed to have anovulatory oligomenorrhea, without excluding pregnancy before each course of therapy; and (3) this drug may be prescribed to women who experience recurrent abortion or infertility because of luteal defects, and many of these women may find oral therapy more pleasant than vaginal suppositories or IM injections. It remains to be shown, however, what dose of oral P provides endometrial protection consistently. Similarly, it

remains to be proven that this therapy is effective in treating luteal phase inadequacy. This investigation addressed neither of these issues.

In summary, 300 mg of P was significantly more effective than placebo in inducing withdrawal bleeding, and side effects were no more frequent during P therapy than during placebo. Endogenous E_2 concentrations could not be used to predict if withdrawal bleeding would occur after P administration, but P concentrations > 3.0, 2.5, or 2.0 ng/mL were of predictive value. No significant changes in lipid concentrations were observed.

REFERENCES

1. Nora AH, Nora JJ: A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch Environ Health 30:17, 1975
2. Yovich JL, Turner SR, Draper R: Medroxyprogesterone acetate therapy in early pregnancy has no apparent fetal effects. Teratology 38:135, 1988
3. Friedewall WT, Levy RJ, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18: 499, 1972
4. Rarick LD, Shangold MM, Ahmed SW: Cervical mucus and serum estradiol as predictors of response to progestin challenge. Fertil Steril 54:353, 1990
5. Kletzky OA, Davajan V, Nakamura RM, Thorneycroft IH, Mishell DR: Clinical categorization of patients with secondary amenorrhea using progesterone-induced uterine bleeding and measurement of serum gonadotropin levels. Am J Obstet Gynecol 121:695, 1975
6. Yen SSC: Chronic anovulation caused by peripheral endocrine disorders. In Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management, 2nd edition, Edited by SSC Yen, RB Jaffe. Philadelphia, W. B. Saunders, 1986, p 449
7. Simon J: Serum pharmacokinetics of oral micronized progesterone in women: feeding effects and comparison with IM progesterone. In Proceedings of the Consensus Development Conference on Progestogens, International Proceedings Journal, Vol. 1, No. 1, Edited by RA Lobo, MI Whitehead. New York, Worldwide Medical Group, 1989, p 31
8. Ottosson UB, Johansson BG, von Schoultz B: Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: a comparison between progestogens and natural progesterone. Am J Obstet Gynecol 151:746, 1985

Attachment 5

SCH 961 CAPSULES 100 MG
CONTROLLED CLINICAL STUDY

STUDY NO. C90-557

Table 1. Study Procedures (Protocol No. C90-557)

	Screening[a]		Estrogen Priming		Double-Blind Treatment		Follow-up	Premature Discontinuation Requirements
Treatment Cycle	0	0	1[b]	2	3	4		
Study Visit	A_0	A_1		B_1	B_2	B_3	F_1	
Cycle Day				6	26	26		
Acceptable Visit Window (Cycle Days)				6-10	24-28	24-28	21-28	
Medical history	X							
Complete physical exam	X					X	(c)	X
Breast exam	X			X	X	X	X	X
Pelvic exam	X			X		X	(c)	X
Blood pressure and heart rate	X	X		X	X	X	X	X
Body weight	X	X		X	X	X	X	X
Height	X							
Mammography	(d)							
Panel 1								
CSC, chemistry, urinalysis	X			X		X	(e)	(e)
Panel 2								
Serum FSH, estradiol, estrone	X			X		X	(e)	(e)
Panel 3								
T_4RIA, T_3RIA, T_3RU, HS-TSH	(f)							
Panel 4								
Pap smear	X					X		
Panel 5								
Serum progesterone		X		X		X	(e)	(e)
Panel 6								
First void AM spot urinary PDG/CR		X		X		X	(e)	(e)
Panel 7								
Lipid profile (T chol, TG, HDL-C, LDL-C and VLDL-C)		X		X		X		
Panel 8								
Endometrial biopsy				X		X	(g)	(e)
Archival sample	X	X		X		X	(h)	(h)
Diary check (vaginal bleeding)		(i)	X	X	X	X	X	X
Reporting of adverse events (adverse experiences & concurrent illnesses)		X	X	X	X	X	X	X
Concomitant medication check	X	X	X	X	X	X	X	X
Distribution of medication		X		X	X	X		
Study medication check				X	X	X	X	X

a: Visit A1 was to occur approximately one to four weeks after Visit A0.
b: No visit during Cycle 1; however, diary, adverse event, and concomitant medication data were collected.
c: To be done only if biopsy was required.
d: Mammography was not to have been done for study purposes until the patient's laboratory results indicated eligibility for study continuation. If one was done within one year of study entry and the report was available, it did not need to be repeated.
e: If clinically indicated.
f: This panel must have been done on all patients on concomitant thyroid replacement hormone.
g: An endometrial biopsy was required if the patient's end of treatment endometrial biopsy results indicated hyperplasia.
h: Sample collected for archive if blood was drawn at this visit.
i: Screening diary data to be evaluated for seven consecutive days immediately before start of Cycle 1.

Attachment 6

Table 8. Noyes Histologic Criteria for Evaluation of Endometrial Secretory Transformation (Progestational Activity) (Protocol No. C90-557).

Noyes Histologic Feature Evaluated		Description	Denotes Secretory Activity
Morphologic Criteria	Proliferative Glands	Early Follicular Pattern Late Follicular Pattern	Not Applicable Not Applicable
	Proliferative Glands With Few Secretory Glands	Present Absent	Yes Not Applicable
	Subnuclear Vacuoles[a]	25-50%[a] 51-100%[a]	Yes Yes
	Late Secretory Glands Without Predecidua	Present Absent	Yes Not Applicable
	Late Secretory Glands With Focal Areas of Predecidua	Present Absent	Yes Not Apolicable
	Late Secretory Glands With Diffuse Predecidua[b]	Present Absent	Yes Not Applicable
	Inactive Glands	Present Absent	No Not Applicable
	Bleeding Features Due to Technique[c]	Present Absent	Not Applicable Not Applicable
Overall Assessment of Progestational Activity Categories		Complete Secretory Activity Partial Secretory Activity No Secretory Activity	Yes Yes No

a: Subnuclear vacuolization is an early sign of progestational activity; 25-50% is consistent with 36-49 hours postovulation, while 51-100% is consistent with 3-4 days postovulation.
b: The maximal progestational effect is seen approximately 11-13 days postovulation.
c: The presence of bleeding was noted as an observation; its absence or presence did not indicate the presence or absence of secretory activity.

Attachment 7

Table 26. Mean Changes From Baseline (Visit B1) at the End of Double-Blind Treatment in the Lipid Profile for the Safety (ITT) Population (Protocol No. C90-557).[a]

	Mean Change From Baseline[b]					p[c]
	SCH 961 100 mg/day N=24	SCH 961 200 mg/day N=22	SCH 961 300 mg/day N=18	SCH 961 400 mg/day N=22	Placebo N=23	
Total Cholesterol (mg/dL)	+5.0	+2.8	-1.5	-1.6	-1.0	0.52
HDL-C (mg/dL)	-1.8	-0.7	-3.9	-3.1	+1.4	0.07
LDL-C (mg/dL)	-0.3	+6.7	-1.1	-4.3	+3.4	0.25
VLDL-C (mg/dL)	+7.0	-3.2	+3.5	+5.9	-5.8	0.05
Triglycerides (mg/dL)	+13.8	-6.7	+19.1	+12.8	-10.0	0.04

Abbreviations:
HDL-C = high density lipoprotein cholesterol
LDL-C = low density lipoprotein cholesterol
VLDL-C = very low density lipoprotein cholesterol

a: More detailed summary tables including percent changes as well as p-values for pairwise comparisons between SCH 961 groups and placebo are in Appendix C-15. Patient listings of lipid readings may be found in Section 11: Case Report Tabulations, Subsection D.

b: All patients also received Premarin® 0.625 mg/day.

c: Overall p-value based on Kruskal-Wallis test.

FEB 7 1990

ORIGINAL

NDA 19-781
Utrogestan

LaSalle Laboratories
February 2, 1990

Medical Officer's Review of Submission
Dated January 30, 1990

Submission dated January 30, 1990 is a response to the issue we raised at our January 22 meeting with the sponsor about the inability of oral, micronized progesterone to elicit secretory changes in the estrogen-primed endometrium which is characteristic of progestins.

At the January 22 meeting we pointed out that the sponsor's study conducted by Dr. Joyce Vargyas of the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

In response the sponsor submits two publications-"by Whitehead, et. al."- which they claim demonstrate that Utrogestan does elicit secretory changes in the endometrium, a conclusion with which they expect we will agree, upon review of the articles.

I. The first publication, which is actually authored by Lane, Siddle, Ryder, Pryse-Davies, King, and Whitehead appeared in B.M.J., Volume 287, October 29, 1983 and is entitled "Dose Dependent Effects of Oral Progesterone on the Oestrogenised Postmenopausal Endometrium".

This article was mentioned in the medical officer's original review of this NDA even though the article had not been submitted or referred to by the sponsor at that time.

In this study of postmenopausal women, all patients received Premarin 1.25 mg daily continuously with the addition of Utrogestan for the first ten days of each calendar month. Seventeen patients took 300 mg of Utrogestan daily; 18 took 200 mg daily; and 15 took 100 mg daily. These doses were chosen

on the basis of the plasma concentrations of progesterone achieved after oral administration. Curettage was performed on every patient using either outpatient Vabra suction curettage or formal dilatation and curettage under general anesthesia in the third or subsequent treatment month on the sixth day of combined treatment for histological, ultrastructural, and biochemical evaluation. Secretory histological changes were induced within the endometrium in a dose dependent manner, as were progesterone sensitive ultrastructural features such as nucleolar channel systems, giant mitochondria, and subnuclear accumulations of glycogen. Dose response relations were also observed for suppression of DNA synthesis and nuclear estrogen receptor, and for induction of the activities of estradiol and isocitric degydrogenases. Suboptimal effects were observed with the lower doses, but Utrogestan 300 mg daily achieved responses approaching and within the physiological range and the authors concluded that 300 mg daily may be effective for therapeutic purposes.

The morphological changes within the endometrium were assessed using a simple scoring system. Subnuclear glycogen is deposited just before and giant mitochondria develop immediately after ovulation in the normal ovulatory cycle. Nucleolar channel systems become visible three days after ovulation and remain for three or four days. The presence of each of these features in the postmenopausal endometrial samples was accorded a score of one point, and no score was give when they were absent. Early secretory changes observed by light microscopy also scored one point, if present.

Endometrium sufficient for assessment by transmission electron microscopy was obtained from seven patients taking 100 mg progesterone, from 11 receiving 200 mg, and from 12 subjects using 300 mg. The table below gives the numbers of samples showing subnuclear accumulations of glycogen, giant mitochondria, and nucleolar channel systems. For example, with 100 mg progesterone three samples contained subnuclear glycogen but giant mitochondria and nucleolar channel systems were absent.

The table below also shows the combined scores for these three ultrastructural features plus the presence of secretory changes observed by light microscopy. The score (number of samples showing feature/number of samples examined) for

progesterone 100 mg was 8/32 (25%), for 200 mg 27/46 (59%), and for 300 mg 35/48 (73%). Comparative data for samples obtained between days 17 and 21 of the secretory phase were 32/32 (100%). None of these features was present in the proliferative phase in premenopausal samples and during the estrogen only phase of postmenopausal estrogen treatment.

Ultrastructural and secretory features in endometrium of postmenopausal women treated with conjugated equine oestrogens 1·25 mg continuously either alone or with progesterone 100 mg, 200 mg, or 300 mg daily added for 10 days each month. Proliferative and secretory phase data for days 17-21 included for comparison

Morphological feature	Proliferative	Secretory (days 17-21)	Conjugated equine oestrogens alone	Conjugated equine oestrogens 1·25 mg daily plus progesterone: 300 mg daily	200 mg daily	100 mg daily
Subnuclear accumulations of glycogen	0/11	8/8	0/14	11/12	9/11	3/7
Giant mitochondria	0/11	8/8	0/14	8/12	6/11	0/7
Nucleolar channel systems	0/11	8/8	0/14	6/12	2/11	0/7
Secretory histology	0/11	8/8	0/14	10/12	10/13	5*/11
Total score (%)	0/44 (0)	32/32 (100)	0/56 (0)	35/48 (73)	27/46 (59)	8/32 (25)

*Includes one sample showing secretory histology and mild atypical hyperplasia.

Progesterone 100 mg produced secretory changes in only five of 11 samplers (45%) and failed to induce giant mitochondria and nucleolar channel systems. The combined score was only 25% (8/32). Three samples (27%) showed mild to moderate atypical hyperplasia (one of these also contained secretory changes).

The 200 mg dose caused secretory transformation in 10 of 13 samples (77%). In nine of these 10 specimens, however, a mixed endometrial pattern was observed, secretory features coexisting with proliferative and non-secretory type glands. Giant mitochondria were observed in six but nucleolar channel systems were seen in only two of the 11 specimens, and the combined score was 59% (27/46).

Progesterone 300 mg produced the best effects, with 10 of the 12 samples (83%) showing secretory transformation. Subnuclear accumulations of glycogen were seen in 11 samples (91%), but giant mitochondria were observed in only eight and nucleolar channel systems in only six of these samples, giving a combined score of 73% (35/48).

Why the ultrastructural responses lacked the degree of uniformity observed with endogenous progesterone which achieved maximum effects in every specimen examined (100%; 32/32) is unclear. In addition, they compared less favorably with the synthetic progestins norethisterone mg and DL-norgestrel micrograms, for which the same authors reported combined scores of 96% and 90% respectively.

The biochemical effects of oral progesterone were similarly dose dependent, suppression of DNA synthesis and nuclear estradiol receptor, which provide an index of antiestrogenic effects of oral progesterone, and induction of enzymatic activity, which assesses the secretory effects, were clearly suboptimal with the 100 mg dose. Values comparable to the premenopausal secretory phase range were induced by progesterone 300 mg. Intermediate effects were observed with the 200 mg dose.

Reasons for the discrepancy between the morphological and biochemical responses to progesterone 300 mg are unclear. With the androgenic progestogens norethisterone and DL norgestrel, the same authors have reported a close correlation between the morphological and biochemical effects. Thus, although oral progesterone undoubtedly exerts an and organ effect within the endometrium, the inability of 300 mg to induce uniform secretory and fine structural features suggests that larger doses may be required. Potential disadvantages to increasing the dose further include the development of adverse physical and psychological effects, whereas a potential advantage might be in increasing the efficiency of regular endometrial shedding.

The combined score of 73% with the 300 mg dosage reported in this paper does not constitute substantial evidence of a good progestational response with micronized progesterone.

II. The second publication, which is authored by King and Whitehead, is entitled "Assessment of the Potency of Orally Administered Progestins in women." The authors analyzed the effects of at least three doses of each of five orally administered progestins on estrogen-primed, postmenopausal endometrial biochemistry and morphologic features. The progestins tested were norethindrone, medroxyprogesterone acetate, norgestrel, dydrogesterone, and progesterone. The dose required to elicit responses similar to those seen in premenopausal, secretory endometria was assessed for each of the parameters measured, and the relative potencies were calculated. Potencies, relative to a value of 1 for norethindrone, are L norgestrel 8 (D/L norgestrel 4), MPA 0.1, dydrogesterone 0.02, and progesterone 0.002.

Figure 2 of the article demonstrates morphologic changes induced in glandular epithelium of estrogen- primed, postmenopausal endometrium by progestins. Dose-response effects were obtained with all of the progestins tested, although suboptimal responses were obtained with MPA and progesterone. Dydrogesterone 20 mg/day evoked a 100% response. Norethindrone 2.5 mg/day evoked a 96% response. D/L norgestrel 0.15 mg/day evoked a 90% response. MPA 5 mg/day evoked only an 83% response and progesterone 300 mg/day evoked only a 70% response.

Table 2 of the article gives the oral dose of progestin required to elicit changes equivalent to the premenopausal secretory phase. For morphological changes, a dose of progesterone higher 300 mg/day is required.

This second paper, likewise, does not provide substantial evidence of a good progestational response with a 300 mg/day dose of micronized progesterone.

It should be noted, also, that on page 3 of the cover letter for this submission the sponsor states that they were informed by division representatives (in the January 22, 1988 meeting) that only a single confirmatory clinical trial in secondary amenorrhea would be necessary for approval of Utrogestan for progestin class labeling. This is not true. The sponsor was told that it should be relatively easy and straight forward to perform a study of women with secondary amenorrhea. This did not imply that a study of amenorrhea would yield anything more than that single indication (secondary amenorrhea).

For the record, the sponsor is also in error in stating on page 3 of the cover letter that their secondary amenorrhea study was completed in accordance with the protocol approved by the agency. The sample size set in the protocol approved by the agency was 75 and the sponsor entered only 64 subjects, two of whom withdrew prior to receiving drug. Two subjects who completed the study were dropped because their hormone levels were outside of 15% of protocol specifications. This resulted in only 60 evaluable subjects including three who had amenorrhea of less than 60 days as called for in the protocol.

Conclusion:

The study by Dr. Vargyas of the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

The two published articles submitted do not provide substantial evidence that micronized progesterone at a dose of 300 mg/day consistedly transforms proliferative endometrium into secretory endometrium.

/S/

Ridgely C. Bennett, M.D., M.P.H.

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ORIGINAL

JAN 18 1990

Medical Officer's Original Review of NDA 19-781

Firm's Name: La Salle Laboratories

Proposed Trade Name: Utrogestan

Established Name: Progesterone (micronized)

Active Ingredient: Progesterone

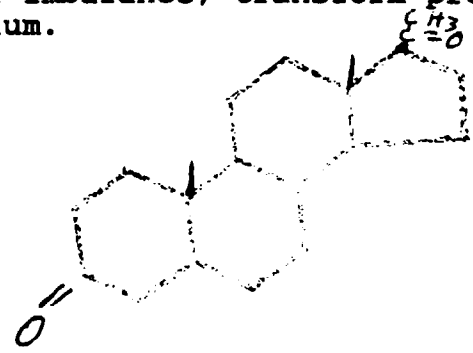
Dosage Form: Capsule

Strength: 100 mg/capsule

Prescription or OTC: Prescription

I. Proposed Uses: Secondary Amenorrhea; abnormal uterine bleeding due to hormonal imbalance; transform proliferative into secretory endometrium.

II. Structural Formula:



III. Dosages Recommended:

A. Secondary Amenorrhea: 200 to 300 mg at bedtime for 5 to 10 days orally.

B. Abnormal Uterine Bleeding Due to Hormonal Imbalance:

Beginning on the calculated 16th or 21st day of the menstrual cycle, 200 to 300 mg at bedtime for 5 to 10 days orally.

C. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 200 to 300 mg daily at bedtime for 10 days orally beginning on the 16th day of the cycle.

IV. Same and Related Drugs: Progesterone, I.M.

V. Pharmacology: Refer to pharmacologist's review dated August 11, 1989.

VI. Pharmacodynamics: Refer to pharmacologist's review dated August 11, 1989.

VII Consultations: None.

VIII. Clinical Studies: A single center, double blind, parallel group, placebo controlled study was conducted at Georgetown University by Dr. James Simon to compare the efficacy and safety of two strengths of Utrogestan with placebo in the initiation of withdrawal bleeding in patients with secondary Amenorrhea.

Secondary Amenorrhea was defined, for the purpose of this protocol, as the failure to have any interval bleeding for more than 60 days in any patient documented to have had prior normal menstrual cycles.

Withdrawal bleeding was defined, for the purpose of this protocol, as any bleeding or blood stained discharge passed per vagina during the withdrawal interval.

Withdrawal interval, for the purpose of this protocol, was defined as the time from the beginning of progesterone therapy up to and including one week following the final dose. This definition was unacceptable to the medical reviewer who recommended that withdrawal interval be defined as the time from the termination of progesterone therapy up to and including one week following the final dose.

Seventy-five completed patients (25 per group) were to be studied.

The following criteria had to be met in order to be included in the study:

A. Normal, healthy, outpatients over the age of 18 years.

B. Patients with secondary amenorrhea of at least 60 days.

C. FSH and LH 40 m I u/ml/ or less.

D. Serum estradiol 60 pg/ml/ or more.

E. Serum progesterone less than 1 ng/m/.

F. Serum hCG levels that are undetectable.

G. Serum dehydroepiandrosterone sulfate 5000 ng/ml/ or less.

H. Serum testosterone 200 ng/dl or less.

Patients to be excluded from study included those who had receive exogenous steroid hormones within the previous 90 days of enrollment in the study.

All patients were to use daily menstrual calendars to document any bleeding or bloodstained discharge.

Patients satisfying all admission criteria were to be randomized to one of the following treatment regimen:

A. Utrogestan 200 mg at bedtime for 10 days.
B. Utrogestan 300 mg at bedtime for 10 days.
C. Placebo at bedtime.

Efficacy of the progesterone therapy was to be determined by comparing both of the Utrogestan groups to the placebo group with respect to the initiation of withdrawal bleeding using a chi-square test.

The sample size determination was based on making one- tailed tests comparing the response rate of each of the Utrogestan treatment groups to that of the placebo group. It was desired that these two comparisons have an overall significance level of alpha = 0.05 so that each comparison would be made at the that each comparison would be made at the alpha 0.025 level of significance. Assuming a 20% response rate for placebo and setting power equal to 80%, sample sizes were determined for the Utrogestan groups having a response rate of 60% and 70%. A response rate of 60% required a total of 81 patients and 70% required 54 patients. The total sample size for the study was set at 75 with 25 patients in each treatment group.

This study was initiated August 31, 1988 and competed February 17, 1989. The report of the clinical study is dated March 3, 1989.

A total of 190 patients were originally screened for the study with only 64 meeting the entry criteria and being acceptable for enrollment into the study Two patients, both in the Utrogestan 200 mg group, withdrew from the study for personal reasons prior to receiving drug. Two patients who completed the study (one in the Utrogestan 200 mg group and one in the Utrogestan 300 mg group) had hormone levels outside of 15% of protocol specifications. This resulted in 60 evaluable patients

including three who had amenorrhea of less than 60 days as called for in the protocol (but who had amenorrhea of more than 50 days).

There were no statistically significant differences between the treatment groups for any baseline variable. Medical history (including time from last menstrual period), physical examination, Pap smear, and baseline laboratory values were all comparable between groups.

Of the 60 evaluable patients, the average age for each treatment group was between 25.7 and 28.7 years with a range of years. There were no statistically significant differences between the three treatment groups in regard to height, weight, blood pressure, or pulse rate. There were no statistically significant differences between treatments with respect to any of the hormones measured.

The sponsor analyzed the data using their definition of withdrawal interval as being the time from the beginning of treatment up to and including one week following the final dose (a total of 17 days) with the following results:

Utrogestan 300 mg		Utrogestan 200 mg		Placebo	
18/20	90%	10/19	53%	5/21	24%

The proportion of patients experiencing withdrawal bleeding with Utrogestan 200 mg was not statistically significantly greater than that of the placebo group while the proportion in the 300 mg group was significantly greater than that of the placebo group.

Days Until Withdrawal Bleeding (Day 10 is end of therapy)
(Each Patient)

Utrogestan 300 mg	Utrogestan 200 mg	Placebo
15	12	16
15	11	15
13	10	8
12	9	7
12	9	6
12	9	
11	9	
11	8	
11	8	
11	2	
11		

10
10
10
10
9
8
2

The mean number of days (counting from initiation of therapy) until withdrawal bleeding was between 8 and 11 days. Therapy consisted of 10 days treatment.

Although a comparison of the two Utrogestan groups was not a planned comparison, a test of equal proportions was performed. There was a statistically significant difference between the two treatments (two -tailed p=0.0253). Nearly twice as many patients in the Utrogestan 300 mg group had withdrawal bleeding compared to the Utrogestan 200 mg. group.

Using the definition of withdrawal bleeding as the time from the termination of progesterone therapy up to and including one week following the final dose resulted in 3 of the 5 patients in the placebo group who bled being excluded from analysis 3 of the 10 patients in the Utrogestan 200 mg group who bled being excluded, and 2 of the 18 patients in the Utrogestan 300 mg group who bed being excluded from analysis. Therefore, the following results were obtained:

Utrogestan 300 mg		Utrogestan 200 mg		Placebo	
16/20	80%	7/19	37%	2/21	10%

The proportion of Patients experiencing withdrawal bleeding with Utrogestan 200 mg was not statistically significantly greater than that of the placebo group (one -tailed p=-.0448). The proportion of patients experiencing withdrawal bleeding with Utrogestan 300 mg was statistically significantly greater than in the placebo group.

The difference between Utrogestan 300 mg and Utrogestan 200 mg was statistically significant.

In addition to the single center study of withdrawal bleeding a single center study entitled "Histological Effects of Sequential Use of Estrogen/Progesterone Therapy on the Endometrium of Postmenopausal Women" was performed by Dr. Joyce Vargyas, Assistant Professor, Obstetrics and Gynecology, University of Southern California Health Sciences. This study was performed under IND Patients were

randomized into two groups of ten women. One group received Premarin 0.625 mg daily for the first 25 days of each month plus Utrogestan 200 mg daily from Days 12 through 25 of each month and the other group received Premarin 1.25 mg daily for the first 25 days of each month plus Utrogestan 200 mg daily from days 12 through 25 of each month. Each patient was treated for a total of 6 months. Endometrial biopsies were performed pretreatment and on day 25 of the third and sixth treatment cycles. Partially developed progestational maturation was found in 15 of 40 post treatment endometrial biopsies. The remaining biopsies showed either weakly proliferative (subprogestational) change or were inadequate for evaluation.

IX Literature Reviewed:Lane, Siddle, Ryder, Pryse-Davies, King, and Whitehead B.M.J. Volume 287 October 29, 1983. "Dose Dependent Effects of Oral Progesterone on the Oestrogenised Postmenopausal Endometrium".

In this study of postmenopausal women, all patients received Premarin 1.25 mg daily continuously with the addition of Utrogestan for the first ten days of each calendar month. Seventeen patients took 300 mg of Utrogestan daily; 18 took 200 mg daily; and 15 took 100 mg daily. These doses were chosen on the basis of the plasma concentrations of progesterone achieved after oral administration. Curettage was performed on every patient using either outpatient Vabra suction curettage or formal dilatation and curettage under general anesthesia in the third or subsequent treatment month on the sixth day of combined treatment for histological, ultrastructural, and biochemical evaluation. Secretory histological changes were induced within the endometrium in a dose dependent manner, as were progesterone sensitive ultrastructural features such as nucleolar channel systems, giant mitochondria, and subnuclear accumulations of glycogen. Dose response relations were also observed for suppression of DNA synthesis and nuclear estrogen receptor, and for induction of the activities of estradiol and isocitric dehydrogenases. Utrogestan 100 mg daily produced secretory changes in only 5 of 11 samples (45%) and Utrogestan 200 mg daily produced secretory changes in 10 of 13 samples (77%). In 9 of these 10 specimen, however, a mixed endometrial pattern was observed, secretory features coexisting with proliferative and non-secretory type glands. Utrogestan 300 mg daily produced the best effects, with 10 of the 12 samples (83%) showing secretory transformation. Suboptimal effects were observed with the lower doses, but Utrogestan 300 mg daily achieved responses approaching and within the physiological range and the

authors concluded that 300 mg daily may be effective for therapeutic purposes.

X. Labeling Evaluation:

XI. Pertinent Conferences and Contacts With Applicant:

A letter was sent to the sponsor August 30, 1989 requesting submission of a summary, analysis, and evaluation of Dr. Vargyas' study.

XII. Conclusions:

The subject of this NDA is micronized progesterone capsules for oral administration. The sponsor is

seeking labeling indications that are identical to those for oral medroxyprogesterone acetate, a derivative of progesterone regarded as safe and effective by FDA.

The sponsor originally stated that in Federal Register volume 36, number 175 (DESI 9238), FDA concluded that preparations containing progesterone are effective for uses in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Actually, FDA evaluated reports received from the National Academy of Science -National Research Council, Drug efficacy study group on progesterone injection, not oral progesterone and the notice states that FDA is prepared to approve new drug applications for progesterone injection. Utrogestan, a Capsule for oral administration, is not covered by this Notice.

The sponsor also stated that they are seeking dosing recommendations for Utrogestan that are identical to those for oral medroxyprogesterone acetate. However, it is noted that medroxprogesterone acetate is not mentioned in DESI 9238 and while medroxyprogesterone acetate is usually administered in doses of 5-10 mg daily, the proposed dose of Utrogestan is 200-300 mg daily. The dosages are obviously not identical, as claimed.

No clinical studies were submitted in support of approval of the application for the indications the sponsor was seeking. A summary of clinical trials involving indications other than those claimed in this application from study reports and published literature was submitted. These clinical trials were irrelevant to this application and included indications for

1) Anovulation or dysovulation
2) Pre-menopausal symptoms
3) Mastodynia and mastopathy
4) Primary or secondary sterility
5) Establishing artificial cycle in menopausal women
6) Premenstrual syndrome
7) Dysmenorrhea
8) Endometriosis
9) Idiopathic orthostatic edema
10) Premature labor

The application was resubmitted and included a single study in patients with secondary Amenorrhea. The sponsor analyzed the results using their (unacceptable

to us) definition of withdrawal interval and reported the following success rates:

Utrogestan 300mg		Utrogestan 200		Placebo	
18/20	90%	10/19	53%	5/21	24%

Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg . The difference between Utrogestan 200 mg and placebo was not statistically significant, but the sponsor concludes that Utrogestan 200 mg and 300 mg both are effective. This certainly is not true. Using the more acceptable defintion of withdrawal bleeding yielded the following success rates:

Utrogestan 300 mg		Utrogestan 200 mg		Placebo	
16/20	80%	7/19	37%	2/21	10%

Again, Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg, and Utrogestan 200 mg was not statistically significantly different from placebo.

The study by Dr. Vargyas of the effects on the endometrium indicated that micronized progesterone at a dose of 200mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

The literature report by Lane et.al. concluded that suboptional effects on the endometrium were observed with daily doses of Utrogestan 100 mg and Utrogestan 200 mg, but that Utrogestan 300 mg daily may be effective for therapeutic purposes.

No studies to support an indication for abnormal uterine bleeding are submitted in this application.

No data is submitted to show that Utrogestan 300 mg daily will transform Proliferative endometrium into secretory endometrium.

The application does not provide substantial evidence of the efficacy of Utrogestan as claimed in the labeling.

XIII. Recommendation: Approval of the application is not recommended.

/S/

Ridgely C Bennett, M.D, M.P.H.

cc: HFD-510
HFD-510 BBennett/ft/cj/11-30-89

1-18-90

IN FILE

NOV 23 1987

NDA 19,781
Utrogestan

Begins Pharmaceuticals Inc.
November 20, 1987

Medical Officer's Original Review

The subject of this NDA is micronized progesterone capsules for oral administration. The sponsor is seeking labeling indications that are identical to those for oral medroxyprogesterone acetate, a derivative of progesterone regarded as safe and effective by FDA.

The sponsor states that in Federal Register volume 36, number 175 (DESI 9238), FDA concluded that preparations containing progesterone are effective for use in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Actually, FDA evaluated reports received from the National Academy of Science - National Research Council, Drug efficacy study group on progesterone injection, not oral progesterone and the notice states that FDA is prepared to approve new drug applications for progesterone injection. Utrogestan, a capsule for oral administration, is not covered by this Notice.

The sponsor also states that they are seeking dosing recommendations for Utrogestan that are identical to those for oral medroxyprogesterone acetate. However, it is noted that medroxyprogesterone acetate is not mentioned in DESI 9238 and while medroxyprogesterone acetate is usually administered in doses of 5-10 mg daily, the proposed dose of Utrogestan is 200-300 mg daily. The dosages are obviously not identical, as claimed.

The results of a study entitled "Utrogestan Clinical Pharmacokinetic Study" is submitted in support of approval of the application. The study goals were:

1) To define blood levels produced by administering Utrogestan with and without food.

2) To quantify the blood levels of progesterone achieved in 15 subjects receiving Utrogestan in comparison to baseline values for progesterone in the same subject.

3) To evaluate the effect on blood levels of progesterone by varying the oral dose of Utrogestan.

4) To compare the blood concentration/time relationship of progesterone levels achieved with Utrogestan and progesterone levels achieved with commercially available IM progesterone.

No clinical studies are submitted in support of approval of the application for the indications the sponsor is seeking. A summary of clinical trials involving indications other than those claimed in this application from study reports and published literature is submitted. These clinical trials are irrelevant to this application and include indications for

1) Anovulation or dysovulation
2) Pre-menopausal symptoms
3) Mastodynia and mastopathy
4) Primary or secondary sterility
5) Establishing artificial cycle in menopausal women
6) Premenstrual syndrome
7) Dysmenorrhea
8) Endometriosis
9) Idiopathic orthostatic edema
10) Premature labor

Conclusion:

No clinical studies are submitted to support the efficacy of the proposed doses of Utrogestan for the claimed indications.

Recommendation:

It is recommended that this NDA not be filed.

/S/

Ridgely C. Bennett, M.D., M.P.H.

Concurrence: PCorfman 11/23/87

NDA Orig
HFN-340
HFN-810
HFN-810/Dr. Bennette/11/23/87/draft/jaf/11/23/87/wang0280