

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-057

MEDICAL REVIEW(S)

Endometrin[®]
(progesterone vaginal insert)
Team Leader Review

NDA: 22057
Drug: Endometrin[®]
(progesterone) Vaginal Insert
Indication: To support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women
Dosage/Form/Route: 100 mg insert administered vaginally twice daily
100 mg insert administered vaginally three times daily
Applicant: Ferring Pharmaceuticals Inc.
Original Submission Stamp Date: August 21, 2006
Primary Review Completion date: June 20, 2007
Date of Final Memorandum: June 21, 2007

Executive Summary:

Progesterone products (including progesterone in oil administered intramuscularly and micronized progesterone compounded as vaginal preparations) have been used since the 1980's as part of the in vitro fertilization treatment-program to supplement corpus luteum progesterone production and support the luteal phase of the artificial cycle as well as an ensuing pregnancy, if this occurs. On May 13, 1997, Crinone[®] 8% /Prochieve[®] (NDA 20-756)) was *Approved* for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency.

In the 2003 Reproductive Health Advisory Committee Meeting, the Division received advice that studies for drug products used for ovulation induction and Assisted Reproductive Technology treatment intended to help women to conceive should study pregnancy as the primary endpoint and focus on pregnancy in the indication. Ferring is seeking approval for two dosing regimens of Endometrin[®] for pregnancy, consistent with the Agency's advice on this indication. During drug development of Endometrin[®] several key recommendations were consistently made by the Division to the Sponsor. These were:

- The indication should emphasize pregnancy through the mechanism of luteal support
- Clinical pregnancy as defined by the presence of a gestational sac and fetal heartbeat should be the primary endpoint for an indication of pregnancy through luteal supplementation

- The study should be conducted as a double blind, double dummy designed trial. If logistically not possible, then at a minimum the investigator **and** ultrasonographer should be blinded
- The primary efficacy analysis should be a two-sided 95% or one sided 97.5% confidence interval between the rates of clinical pregnancy obtained with Endometrin[®] and an approved active comparator
- Even though the Division believes that a non-inferiority limit to the lower bounds of the 95% confidence interval of the difference between Endometrin[®] and comparator should be 6 to 8%, the Division accepts a non-inferiority limit for the inferiority analysis consistent with the 10% non-inferiority limit on pregnancy rate accepted for the approval of Menopur[®]
- Randomization and analyses should be stratified and powered for subgroup analyses of ovarian reserve as measured by Day 3 serum FSH and age of the female partner

The Sponsor essentially followed the Division's recommendation with respect to the indication, the primary endpoint of interest, the non-inferiority design with comparison to an active comparator and the non-inferiority limit to the lower bounds of the 95% confidence interval of the difference between Endometrin[®] and comparator. However, the Sponsor failed to follow the Division's recommendation on blinding of the trial and on stratifying and powering the study to show efficacy differences in the sub-group analyses. The Division believes that the double-blind or at least an investigator-blind design was necessary to minimize the introduction of investigator/physician biases at any of the multiple steps of decision making that occur during an in-vitro fertilization treatment cycle. Randomization after oocyte-retrieval certainly provides for fewer steps for the introduction of investigator bias than would be the case with randomization at the start of the cycle, but nevertheless the opportunity to inappropriately influence the outcome still exists. A double-blind trial design as recommended by a 2003 Reproductive Health Advisory Committee, minimizes the opportunity to purposely manipulate the outcome of the trial.

The female infertility patient's age and ovarian reserve status (as measured by serum FSH level) are two critically important factors in determining the outcome of ovulation induction and in vitro fertilization/embryo transfer. Women of advanced reproductive age (greater than equal to 35 years of age) and poor ovarian reserve represent a different patient population from that of women under age 35 who undergo these procedures. Studies have generally suggested that basal FSH is an even better predictor than age of the outcome of in vitro fertilization. Women greater or equal to 35 years of age comprise an ever increasing proportion of women undergoing in vitro fertilization/embryo-transfer in the U.S. According to the 2004 Assisted Reproductive Technology Success Rates – National Summary and Fertility Clinic Reports published in 2006 by the Centers For Disease Control And Prevention, approximately 60% of all Assisted Reproductive Technology procedures are in women 35 years of age and older. Taking these statistics into account, it is incumbent that the Agency obtains efficacy and safety data in this age sub-group of ovulation induction and in vitro fertilization/embryo transfer –treated subjects before drug products go to market. To that end, the Division has been advising

Sponsors since 2003 that their ovulation induction and in vitro fertilization/embryo transfer trials should be stratified at randomization and the analyses should be stratified and powered to demonstrate true differences, if they exist. This advice was given on multiple occasions to the Sponsor of Endometrin[®]. References to stratification and powering of the analysis for age and ovarian reserve were made in Advice letters dated October 22, 2004 and February 8, 2005, at the End-of Phase 2 Meeting on February 28, and in an Advice letter dated September 9, 2005 in response to the Statistical Analysis Plan for Study 2004-02. The Sponsor stratified randomization using an electronic system at baseline. However, the Sponsor failed to power the study sufficiently so that definitive statistical analyses results could be obtained on sub-groups.

The result of the efficacy analyses for all subjects demonstrated that the ongoing pregnancy rates for Endometrin[®] 100 mg twice daily and 100 mg three times daily were 38.6% and 42.3%, respectively compared to 42.2% rate for Crinone[®] 8%. Further, the lower bounds of the 95% confidence interval of the difference between Endometrin[®] 100 mg twice daily and Crinone[®] 8% (-10.3%) and between Endometrin[®] 100 mg three times daily and Crinone[®] 8% (-6.7%) excludes a difference larger than 10%. Therefore, efficacy was demonstrated in the overall population receiving both Endometrin[®] 100 mg twice daily and Endometrin[®] 100 mg three times daily in that the ongoing pregnancy rate for both dosage regimens of Endometrin[®] were no worse than 10% lower than the ongoing pregnancy rate for the comparator Crinone[®] 8% and non-inferiority was established. The results of the sub-group analyses show that for the population of subjects less than 35 years of age, the ongoing pregnancy rates for Endometrin[®] 100 mg twice daily and 100 mg three times daily were 44.9% and 47.4%, respectively compared to 44.4% rate for Crinone[®] 8%. The lower bounds of the 95% confidence interval of the difference between Endometrin[®] 100 mg twice daily and Crinone[®] 8% (-8.4%) and between Endometrin[®] 100 mg three times daily and Crinone[®] 8% (-5.9%) exclude a difference larger than 10%. However, the results demonstrated with subjects 35-42 years of age and older do not suggest non-inferiority of Endometrin[®] to Crinone[®] 8%. The individual age strata were not sufficiently powered (please refer to the preceding discussion), therefore the Division performed an analysis based on the population of subjects who were age 35-42 years of age as a combined group. This analysis demonstrated that for subjects 35-42 years of age, the ongoing pregnancy rates for Endometrin[®] 100 mg twice daily and 100 mg three times daily were 28.7% and 34.4%, respectively compared to 38.8% rate for Crinone[®] 8%. The lower bounds of the 95% confidence interval of the difference between Endometrin[®] 100 mg twice daily and Crinone[®] 8% (-20.3%) and between Endometrin[®] 100 mg three times daily and Crinone[®] 8% (-14.9%) did not exclude a difference greater than 10%. Therefore, one can not conclude based on this data that Endometrin[®] 100 mg twice times daily and Endometrin[®] 100 mg three times daily is efficacious in the population of women age 35-42. Similarly one can not conclude efficacy for Endometrin[®] in women with serum FSH between 10-15 IU/L, based on the failure of the lower bound of the 95% confidence interval of the difference between Endometrin[®] and Crinone[®] 8% to exclude a difference that is greater than 10% worse.

There were no deaths and 22 Endometrin[®]-treated subjects had serious adverse events in Study 2004-02. Treatment-emergent adverse events in Study 2004-02 were consistent with other trials conducted for ART regimens in which gonadotropins for ovarian stimulation and luteal support drug products are administered. There were no concerning safety signals for either dosing regimen of Endometrin[®].

I recommend that that Endometrin[®] 100 mg twice times daily and Endometrin[®] 100 mg three times daily receive approval to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. I further recommend that the label clearly display, not only the efficacy analyses for the overall group of all subjects studied, but the sub-group efficacy analysis as well. The Dosage and Administration section should reflect the data. Women under the age of 35 can be directed to take either the Endometrin[®] 100 mg twice times daily or the Endometrin[®] 100 mg three times daily dosing regimen. The Dosage and Administration section should inform women over the age of 35 that efficacy in women 35 years of age and older has not been clearly established and an appropriate (or recommended) dose of Endometrin[®] has not been determined. The Dosage and Administration section should not direct or imply that women over the age of 35 should take the Endometrin[®] 100 mg three times daily dosing regimen. The labeling recommendations from the Division provided to and accepted by the Sponsor on June 20, 2007 accomplish these goals. See label attached to this review.

Finally, because the Study 2004-02 was not appropriately powered to provide definitive efficacy results and because there is the question of whether or not some of the age subgroups would have demonstrated efficacy had the study been appropriately powered, I recommend that the Sponsor clarify these issues with a Phase 4 study to establish efficacy, the appropriate dosing regimen and safety in women greater than or equal to age 35 up to age 45. The clinical study should be designed as a non-inferiority comparison to Crinone[®] 8%/Prochieve[®]. Other details of the study should be discussed with and agreed upon by the Agency before the study is initiated.

Background and Regulatory History

The Sponsor began clinical development for Endometrin[®] with a pre-IND meeting held with the Division on October 23, 2003. The Sponsor subsequently submitted both a Phase I protocol and Study 2004-02 for review (Letter Date May 14, 2004). In an Advice letter dated October 22, 2004, the Division provided the Sponsor with the following key comments on Study Protocol 2004-02:

- Recommend that you use a progesterone product that is approved (for this purpose) in Assisted Reproductive Technologies as a comparator.
- Recommend that you perform the study in a double-blind manner utilizing a double dummy
- Recommend that the primary endpoint be clinical pregnancy and be defined by the presence of a gestational sac and fetal heartbeat beginning at six weeks after human chorionic gonadotropin has been administered to induce final follicular maturation.

- Recommend that the primary efficacy analysis be a two-sided 95% or one-sided 97.5% confidence interval analysis of the difference between the rates of clinical pregnancy obtained with Endometrin[®] versus a comparator. The lower bound of the confidence interval should exclude a difference greater than 6% in favor of the comparator.
- Recommend that randomization and analyses be stratified and powered by ovarian reserve as measured by Day 3 serum FSH and age of the female partner.

An End-of-Phase (EOP) 2 meeting was held on February 28, 2005 to discuss preliminary results of the pharmacokinetic study (2004-01) and additional study design and statistical issues for Study 2004-02. The following presents the discussion at this meeting:

1. We remind you of our previous recommendations (Advice letter dated 22-Oct-04) regarding a proposed clinical trial with the primary endpoint of clinical pregnancy rate. Of these recommendations, the following were not addressed in the protocol contained in your briefing document :
 - The study investigator should be blinded to the treatment (assessor-blind). No individual who is making any decisions (investigator or ultrasonographer should be aware of treatment). We recommend using a clinical nurse and consulting safety gynecologist.
 - We recommend that you exclude subjects with a body mass index (BMI) > 38kg/m²
 - We recommend you record detailed past obstetrical history including: gravidity, parity, previous abortions, and ectopic pregnancies.
 - We recommend that you provide a standard method (grading) of determining the severity of ovarian hyperstimulation syndrome (both in terms of what criteria would lead to cancellation and what would be considered a serious adverse event) to allow uniformity between sites.

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You mention that the subject sample size to accomplish our previously recommended non-inferiority limit of 6 % would be larger than that required for approval of the comparator Crinone[®] 8% (May 13, 1997) and other (infertility) drug products presented to the FDA. We do not dispute this. However, in September 2003 we received the Reproductive Health Advisory Committee's recommendation that we should look at the endpoint of clinical pregnancy in our evaluation of gonadotropin drug products used to help infertile women to conceive. This is a departure from the previous approval requirements for gonadotropins and requires a larger sample size. Even more recently on October

29, 2004, we granted approval of your drug product Menopur[®] administered by subcutaneous injection (NDA 21-663) based upon Study MFK/IVF/0399E (protocol not presented to the FDA for review) that evaluated a total of 727 subjects (373 in the Menopur[®] arm and 354 in the comparator arm) for the primary endpoint of clinical pregnancy rate. In this study, for which agreements were made prior to the Advisory Committee, the pre-specified non-inferiority limit (for which the lower-bound of the 95% confidence interval could not exceed) was a difference of 10%. The lower bound of the 95% confidence interval of the difference by your analysis was -3.3 thus excluding that the difference in pregnancy rate between Menopur[®] and the comparator was greater than 10% in favor of the comparator. The Division does not wish to lower the standard for demonstration of efficacy for Endometrin[®] relative to this recent (2004) approval of Menopur[®].

The Division notes that at the September 29, 2003 Advisory Committee meeting, Dr. Emerson made some calculations on the lower acceptable limit of the 95% confidence interval of clinical pregnancy rate based on data from previously approved gonadotropin or menotropins drug products. The Division's clinical team interpreted this as a recommendation by Dr. Emerson that the difference between products should be no greater than this value of 6% (or 8%). We note that it is not entirely clear to us that this recommendation was tied only to an approximately 20% expected clinical pregnancy rate. We have sought clarification from Dr. Emerson regarding his calculations and whether these would be adjusted with a background rate of 30% as opposed to 20%.

Given all of the preceding information, we continue to recommend a tighter noninferiority limit of 6%-8% on the difference in clinical pregnancy rate. Most importantly, we do not feel that the bar for efficacy demonstration of this product should be lower than for your recently approved Menopur[®] which represents an application that is close to our thinking on these drug products. Remember, that these are our recommendations (guidance) and represent our thoughts relative to demonstration of efficacy.

In view of the difference in interpretation of the recommendation in the Advisory Committee transcript, we would be willing to allow (i.e., before publication of a draft guidance), a pre-specified 10% difference as the lower limit of the 95% Confidence Interval such as in the Menopur[®] Study MFK/IVF/0399E.

If after this discussion, we can not agree on a non-inferiority limit we invite you to submit your protocol as a special protocol assessment and we will seek the input of one or more SGE consultants.

3. We recommend that randomization and analyses be stratified and powered for subgroup analyses of ovarian reserve as measured by Day 3 serum FSH, age of the female partner and the type of insemination occurring [i.e. conventional in-vitro fertilization (IVF) vs. intracytoplasmic sperm injection (ICSI)]. We further recommend a sub-stratification of data based on body mass index (BMI) and

infertility diagnosis. The analysis of data relative to sub-stratification groups can be descriptive. Studies should be powered to demonstrate differences in these (substratification) groups only if specific claims regarding these groups are sought.

4) Additional General comments:

- Standardize the criteria for human chorionic gonadotropin administration.
- Standardize the criteria for down-regulation for all centers.
- Exclude subjects that use additional hormonal drug products (including progesterone creams, other steroid drug products including hydrocortisone) from these phase 3 protocols.
- Provide justification for the exclusion of GnRH antagonists which are the only approved drugs for (prevention of premature LH surge). Exclusion of these drug products may be a labeling issue.
- Clarify whether daily or depot gonadotropin releasing hormone agonists will be used. In study MFK/IVF/0399E submitted to NDA 21-663, it appeared that there were clinical differences in pregnancy rates seen with the various preparations of these agonists.
- We recommend that if you plan on allowing daily and depot gonadotropin releasing hormone agonists in these protocols, that these subjects be stratified.
- Provide justification for the use of the combination of Repronex® and Bravelle® in these protocols. This may impact labeling for Endometrin®.
- Clarify how the IVRS system will perform the randomization in more detail.
- Standardize your terminology of clinical and ongoing pregnancy in both protocols. We recommend that the term clinical pregnancy refer to a pregnancy defined by the presence of a gestational sac and fetal heartbeat beginning at six weeks post embryo transfer.

The Sponsor submitted a revised protocol and statistical analysis plan for Study 2004-02 in Amendments 023 and 024 (dated April 25, 2005 and June 24, 2005). The following *additional* clinical and statistical comments on the revised phase 3 protocol for Study 2004-02 were provided in an Advice letter dated September 12, 2005.

1. The protocol must distinguish between subjects who are withdrawn from the study and subjects who are withdrawn from study medication. To detect all ongoing pregnancies, subjects need to be followed for ten weeks regardless of treatment status.
2. Withdrawing a subject due to noncompliance is discouraged because all subjects will be included in an intent-to-treat analysis.
3. The primary efficacy variable is “ongoing pregnancy following one treatment cycle in the efficacy population.” Consistent with this definition, all subjects need to be followed even if study medication has been discontinued. Potentially, some subjects may become pregnant without treatment. These pregnancies need to be identified and included in an intent-to-treat analysis.
4. In the cover sheet preceding the study protocol, bullet #4 states that “the randomization and analysis is stratified for subgroup analysis of ovarian reserve (Day 3 FSH) and age.” The study protocol, however, does not mention

- stratification and suggests the randomization and analysis will not be stratified. This discrepancy between the cover sheet and the protocol must be resolved.
5. The proposed step-down procedure could prove problematic if the comparison between Endometrin[®] 100mg TID and Crinone[®] 8% fail to meet the non-inferiority margin of 10%, and the comparison for Endometrin[®] 100mg BID appears non-inferior at a nominal Type I level of 5% (two-sided). In such a scenario, we would conclude neither dose of Endometrin[®] was shown to be non-inferior to Crinone 8%.
 6. Instead of a step-down procedure, we suggest increasing the sample size and using a multiple comparison procedure that will allow the testing of each Endometrin[®] dose versus Crinone[®] 8%.
 7. The statistical analysis plan specifies an algorithm for combining small sites. We suggest using a criteria based on characteristics of the sites like, for example, type of IVF protocol, type of clinical site, or geographic location.

A pre-NDA meeting was held on 31-May-06. At this meeting, the Sponsor informed the Division of their plans to submit the results of a PK/PD study (2004-01) and one Phase 3 clinical study (Study 2004-02) to support the filing of the NDA.

The clinical development program for Endometrin[®] 100 mg (progesterone) Vaginal Insert resulted in the conduct of one Phase 3, assessor-blind, 10-week, active-controlled clinical trial, Study 2004-02. Study 2004-02 was performed as the primary study to demonstrate safety and efficacy for Endometrin[®]. Two additional Phase 1 studies (Studies 2004-01 and 2005-08) were also conducted at the request of the Agency to address the following issues:

1. A dose-ranging pharmacokinetic study to evaluate three dosages and two dosage regimens of Endometrin[®] on endometrial development and determine the onset of steady-state (Study 2004-01).
2. A phase 1 pharmacokinetic study to evaluate the pharmacologic parameters of two dose regimens of Endometrin[®] (Study 2005-08)

With this application, the Sponsor is seeking approval of two dosage regimens of 100 mg Endometrin[®] (100 mg twice daily and 100 mg three times daily progesterone vaginal insert) for the indication of pregnancy through progesterone supplementation as part of an Assisted Reproductive Technology treatment program for _____ The application was received August 21, 2006 and was administratively filed on October 20, 2006.

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Clinical

The application is supported by a single Phase 3 clinical trial and two Phase 1 studies.

Study 2004-02

Phase 3 Study 2004-02 was a multi-center, randomized, assessor-blinded, 10-week study conducted to determine the efficacy of Endometrin[®] administered vaginally in terms of ongoing pregnancy rates in women undergoing in vitro fertilization. The study was conducted between July 18, 2005 and April 11, 2006. No subjects were enrolled under

the original study protocol. Two protocols amendments were received. Protocol Amendment 1, dated June 17, 2005 (prior to the start of subject enrollment), extended the window of randomization from one day to two days, increased the window for Study Visits 3 and 5A to 5 days, modified the inclusion/exclusion criteria, and allowed assisted hatching and intracytoplasmic injection. Protocol Amendment 2, dated January 13, 2006 (after the start of subject enrollment), clarified that at least 990 subjects would be enrolled (with at least 330 per treatment group), increased the cap for study center enrollment from 100 to 150 and defined the per protocol population as subjects that were in the efficacy population without major protocol violations (including those that didn't take any additional medications for luteal support that would influence the luteal phase). A total of 1211 healthy infertile women were randomized at 25 clinical sites to one of three treatment groups 100 mg of Endometrin[®] twice daily, 100 mg of Endometrin[®] three times daily and Crinone[®] 8% (90 mg of progesterone) once daily in a 1:1:1 fashion. Subjects were randomized after egg retrieval so that results were given as per retrieval and not as per cycle values. Subjects were stratified at baseline for age of the subject and ovarian reserve.

Inclusion and Exclusion criteria, with exception of those based on BMI, were consistent with previous advice and were acceptable. The label should reflect that subjects over 34 kg/ m² were not studied.

Efficacy

The primary efficacy endpoint for Study 2004-02 was ongoing pregnancy (defined as identification of fetal heart movement at approximately 6 weeks of gestation).

The ITT group (subjects that completed screening, down-regulation, ovarian stimulation, egg retrieval and randomization) was used for evaluation of the Endometrin[®]. The primary endpoint (ongoing pregnancy) across the treatment groups was analyzed using a two-sided 95% confidence interval with a pre-specified non-inferiority margin of 10%. No adjustment was made for multiple comparisons as a step-down procedure was used in the comparison of Endometrin[®] to Crinone[®] 8%. Pregnancy rates between Endometrin[®] three times daily were compared to Crinone[®] 8%. If non-inferiority (10% lower bound relative to Crinone[®] 8%) was substantiated from the comparison, then the pregnancy rate for Endometrin[®] twice daily was compared to Crinone[®] 8%. The results of Study 2004-02 for the ITT population are shown in Table 1 [Derived from Medical Officer Review (MOR) Table 1]:

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Table 1: Analysis of Ongoing Pregnancy Rate per Retrieval for the ITT population

	Endometrin® 100mg BID	Endometrin® 100 mg TID	Crinone® 8% Once Daily
Number of subjects	404	404	403
Ongoing pregnancy rate (OPR) - n (%)	156 (38.6%)	171 (42.3%)	170 (42.2%)
95% Confidence Interval (CI) of OPR	[33.8,43.6]	[37.5,47.3]	[37.3,47.2]
Difference in OPR for Endometrin® and Crinone®	-3.6%	0.1%	
lower bound of 95% CI for difference in OPR	-10.3	-6.7	

Adapted from original source - NDA 22-057/S-000, Final Report, Table 15, page 62 of 7469.

The lower bound of the 95% Confidence Interval of the difference between the ongoing pregnancy rate achieved with the 100 mg Endometrin® three times daily dosing regimen and that achieved with Crinone® 8% was -6.7 and thus non-inferiority was established as this rate was less than the 10% non-inferiority limit. The lower bound of the 95% Confidence Interval of the difference between the ongoing pregnancy rate achieved with the 100 mg Endometrin® twice daily dosing regimen and that achieved with Crinone® 8% was -10.3 and, thus, non-inferiority was established as this rate was at the 10% non-inferiority limit.

In order to provide the consumer with some information on the effects of age and ovarian reserve (the two most important factors influencing the outcome of Assisted Reproductive Technology) on the outcome of pregnancy following luteal and early pregnancy supplementation with Endometrin, the Division advised the Sponsor to stratify the randomization by age and FSH level (measure of ovarian reserve) and to stratify and power the analyses by these subgroups. The Sponsor complied with stratification at randomization only. The Sponsor did not prospectively appropriately power the individual age strata sub-group analyses. The results by age and FSH (ovarian reserve) are shown in Table 2 (MOR Table 2).

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Table 2: Sub-Group Analyses of Ongoing Pregnancy Rate per Oocyte Retrieval by Age Sub-bands and Baseline Serum FSH Evaluation

	Endometrin® 100mg BID (ITT N=404)	Endometrin® 100 mg TID (ITT N=404)	Crinone® 8% once daily (ITT N=403)
<u>Subjects < 35 years old</u>			
(n)	247	247	243
Ongoing pregnancy rate (OPR) - n (%)	111 (44.9%)	117 (47.4%)	108 (44.4%)
95% Confidence Interval (CI) of OPR	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference in OPR for Endometrin® and Crinone® 8%	0.5%	2.9%	
lower bound of 95% CI for difference in OPR	-8.4%	-5.9	
<u>Subjects 35 – 37 years old</u>			
(n)	89	93	98
OPR - n (%)	27 (30.3%)	37 (39.8%)	41 (41.8%)
95% CI of OPR	[21.0, 41.0]	[29.8, 50.5]	[31.9, 52.2]
Difference in OPR for Endometrin® and Crinone® 8%	-11.5%	-2.1%	
lower bound of 95% CI for difference in OPR	-25.2	-16.0	
<u>Subjects 38-40 years old</u>			
(n)	55	46	53
OPR - n (%)	16 (29.1%)	12 (26.1%)	16 (30.2%)
95% CI of OPR	[17.6, 42.9]	[14.3, 41.1]	[18.3, 44.3]
Difference in OPR for Endometrin® and Crinone® 8%	-1.1%	-4.1%	
lower bound of 95% CI for difference in OPR	-18.3	-21.8	
<u>Subjects 41-42 years old</u>			
(n)	13	18	9
OPR - n (%)	2 (15.4%)	5 (27.8%)	5 (55.6%)
95% CI of OPR	[1.9, 45.4]	[9.7, 53.5]	[21.2, 86.3]
Difference in OPR for Endometrin® and Crinone® 8%	-40.2%	-27.8%	
lower bound of 95% CI for difference in OPR	-78.1	-66.3	
<u>Subjects with FSH < 10 IU/L</u>			
(n)	350	347	350
OPR - n (%)	140 (40.0%)	150 (43.2%)	147 (42.0%)
95% CI of OPR	[34.8, 45.3]	[37.9, 48.6]	[36.8, 47.4]
Difference in OPR for Endometrin® and Crinone® 8%	-2.0%	1.2%	
lower bound of 95% CI for difference in OPR	-9.3	-6.1	
<u>Subjects with FSH 10-15 IU/L</u>			
(n)	46	51	49
OPR - n (%)	16 (34.8%)	20 (39.2%)	23(46.9%)
95% CI of OPR	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
Difference in OPR for Endometrin® and Crinone® 8%	-12.2%	-7.7%	
lower bound of 95% CI for difference in OPR	-31.8	-27.1	

Adapted from original source - NDA 22-057/S-000, Final Report, Table 17, page 65 and Table 14.2.2.2, page 190 of 7469.

The results of the sub-group analyses show that for the population of subjects less than 35 years of age or subjects with FSH less than 10 IU/L, the lower bounds of the 95% confidence interval of the difference between Endometrin® 100 mg twice daily and Crinone® 8% and between Endometrin® 100 mg three times daily and Crinone® 8% exclude a difference larger than 10%. Of note the ongoing pregnancy rates of the various age bands for subjects 35 years of age and older and the ongoing pregnancy rate of subjects with a serum FSH between 10 to 15 IU/L following the twice daily treatment regimen and the three times daily treatment regimen with Endometrin were inferior (data did not meet the criteria for non-inferiority) to the ongoing pregnancy rate obtained with Crinone® 8%.

The Division looked at an analysis grouping the age strata as less than 35 years of age and 35 year of age and older in order to provide more subjects for analysis in the latter group. The results of that analysis is provided in Table 3 (MOR Table 3)

Table 3: Sub-Group Analyses of Ongoing Pregnancy Rate per Oocyte Retrieval by Age Grouped as less than 35 years of age and 35 year – 42 years of age

Ongoing pregnancy per retrieval	Endometrin® 100 mg BID N=404	Endometrin 100 mg TID N=404	Crinone® 8% once daily (ITT N=403)
<u>Subjects < 35 years of age</u>			
(n)	247	247	243
Ongoing pregnancy rate (OPR) - n (%)	111 (44.9%)	117 (47.4%)	108 (44.4%)
95% Confidence Interval (CI) of OPR	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference in OPR for Endometrin® and Crinone® 8%	0.5%	2.9%	--
lower bound of 95% CI for difference in OPR	-8.4	-5.9	--
<u>Subjects 35-42 years of age</u>			
(n)	157	157	160
OPR - n (%)	45 (28.7%)	54 (34.4%)	62 (38.8%)
95% CI	[21.7, 36.4]	[27.0, 42.4]	[31.2, 46.8]
Difference in OPR for Endometrin® and Crinone® 8%	-10.1%	-4.4%	--
lower bound of 95% CI for difference in OPR	[-20.3]	[-14.9]	--

This analysis demonstrated that for subjects 35-42 years of age, the lower bounds of the 95% confidence interval of the difference in ongoing pregnancy rates between Endometrin® 100 mg twice daily and Crinone® 8% and between Endometrin® 100 mg three times daily and Crinone® 8% did not exclude a difference greater than 10%. Therefore, one can not conclude based on this data that Endometrin® 100 mg twice times daily and Endometrin® 100 mg three times daily is efficacious in the population of women age 35-42.

Safety

The safety database represents 884 total subjects in three clinical studies (Study 2004-02-Phase 3 and Phase 1 Studies 2004-01 and 2005-08) that were treated with 100 mg of Endometrin[®]. All of the Endometrin[®]-treated subjects received the to-be-marketed products.

Phase 3 Study 2004-02, which provided the primary safety database, included 808 subjects who received one of two dosing regimens of Endometrin[®] (100 mg twice daily or 100 mg three times daily).

The two Phase 1 Studies (2004-01 and 2005-08) evaluated a total of 76 subjects (60 healthy pre-menopausal female subjects that used Endometrin[®]) and provided additional limited safety information with short-term use (10 days of treatment or less).

No deaths occurred during or following the conduct of Phase 3 Study 2004-02 or the two Phase 1 Studies (2004-01 and 2005-08).

In Study 2004-02 1, serious adverse events (SEAs) requiring hospitalization occurred in 22 subjects treated with Endometrin [14 subjects (3%) in the 100 mg twice daily Endometrin[®] group and 8 (2%) in the 100 mg three times daily Endometrin[®] group]. Nine subjects [9 (2%)] of the Crinone[®] 8% -treated subjects had a serious adverse events. The 14 serious adverse events occurring in 14 subjects in the 100mg twice daily Endometrin[®] group included one DVT, one case of thyroid cancer, one case of cholecystitis and cholelithiasis, one case of abdominal pain of uncertain etiology, seven cases of ovarian hyperstimulation syndrome (OHSS); two cases of ovarian torsion, and one ectopic pregnancy. Eight serious adverse events occurred in 8 subjects treated with Endometrin 100 mg three times daily. These included: 6 cases of OHSS, one post-surgical (D& C) complication and one case of subchorionic hematoma in diamnionic pregnancy.

Three of the serious adverse events resulted in discontinuation of Endometrin[®] [ovarian torsion (subject 09012) in the Endometrin[®] 100 mg twice daily group, 2 severe ovarian hyperstimulation cases (subject 11007 and 17030) in the Endometrin[®] three times daily group]. The three serious adverse events that resulted in discontinuation were determined to be unrelated to Endometrin[®]. There was no clinically significant difference between treatment groups in the percentage of subjects who completed Study 2004-02. OHSS was the primary cause of discontinuation for SAEs and the percentage discontinuing for this reason was similar across the three treatment groups.

The percentage of treatment-emergent adverse events (TEAEs) appeared similar in the groups treated with the 100 mg twice daily and 100 mg three times daily Endometrin[®] regimens and in the group treated with Crinone[®] 8%; the percentages were 53.2%, 53.7% and 52.1 %, respectively. The most frequent TEAEs in the three groups were: Post-oocyte retrieval pain (28% in the Endometrin[®] 100 mg twice daily group, 25% in the

Endometrin[®] 100 mg three times daily group and 25% in Crinone[®] 8%), abdominal pain (11% in the Endometrin[®] 100 mg twice daily group, 11% in the Endometrin[®] 100 mg three times daily group and 15% in Crinone[®] 8%), nausea (8% in the Endometrin[®] 100 mg twice daily group, 7% in the Endometrin[®] 100 mg three times daily group and 8% in Crinone[®] 8% and OHSS (7% in the Endometrin[®] 100 mg twice daily group, 7% in the Endometrin[®] 100 mg three times daily group and 6% in Crinone[®] 8%). The percentages of these TEAEs are not concerning when compared to the percentage of TEAEs seen in similar ART studies.

Pregnancy Information

The livebirth rates per treatment assignments were 35%, 38% and 38% in the Endometrin[®] 100 mg twice daily group, Endometrin[®] 100 mg three times daily group, and the Crinone[®] 8% group, respectively. The livebirth rates seen with the two Endometrin[®] treatment arms are consistent with the reported 2002 livebirths per retrieval rate of 31.6% in the general Assisted Reproductive Technology population in 2004. The multiple pregnancy rates as percentages of the ongoing pregnancies were 46%, 46% and 39% in the Endometrin[®] 100 mg twice daily group, Endometrin[®] 100 mg three times daily group, and the Crinone[®] 8% group, respectively. The multiple pregnancy rates appeared to be somewhat higher in the Endometrin[®] groups though not higher than expected in an Assisted Reproductive Technology treatment program. There were no higher order pregnancies above triplets.

A total of 16 neonates of 643 livebirths were born with birth defects (2.5%). In the individual treatment arms, the fetal birth defect rates were 3.4%, 3.1% and 0.9% in the Endometrin[®] 100 mg twice daily group, Endometrin[®] 100 mg three times daily group, and the Crinone[®] 8% group, respectively. See the primary MOR for details on the description of reporter birth defects. The rate in the Endometrin[®] groups are numerically higher than in the Crinone[®] 8% group, but not abnormally elevated over the 5-8% reported background rates for defects in babies born following Assisted Reproductive Technology procedures.

DSI

Three sites were identified for a Division of Scientific Investigations (DSI) audit of the Sponsor's data and/or analyses. The audit results are as follows:

1. Vicki Schnell, MD (Site 19)
Center for Reproductive Medicine
450 Medical Center Blvd Suite 202
Webster, TX 77598
Conclusion: The final classification for this site was No deviation from regulations – data acceptable (NAI).
2. Mostafa Abuzeid, MD (Site 26)
IVF Michigan
3950 S. Rochester Rd

Rochester Hills, MI 48307

Conclusion: The final classification for this site was VAI – No Response

Requested – Data acceptable

3. Kevin Doody, MD (Site 05)

Center for Assisted Reproduction

1701 Park Place Ave

Bedford, TX 76022

Conclusion: The final classification for this site was No deviation from regulations – data acceptable (NAI).

Clinical Pharmacology

This submission contains two Phase 1 studies, PK/PD Study 2004-01 and PK Study 2005-08. Dose selection for Phase 3 Study 2004-02 was supported using PK/PD data on serum progesterone levels and transformation of the endometrium to a secretory state. Single-dose and multiple-dose PK of progesterone from Endometrin[®] vaginal tablets were assessed in Study 2004-01 and 2005-08.

In Study 2004-01, progesterone vaginal insert at single doses of 50, 100 and 200 mg daily and 100 mg and 200 mg twice daily, as well as, intramuscular progesterone 50 mg daily were studied in healthy volunteers. Endometrin[®] dose regimens of 100 mg twice daily and 200 mg twice daily demonstrated steady state mean C_{avg} values of 7.47 and 8.31 ng/ml, respectively. The mean C_{avg} of intramuscular progesterone was 18 ng/ml. The administration of the 100 mg twice daily regimen of Endometrin[®] (one of the two proposed regimens) to healthy premenopausal women who were down-regulated with Lupron[®] resulted in a steady-state C_{max} of 13.2 ± 8.3 ng/ml and a mean C_{avg} of 7.47 ng/ml, which was below the target concentration of 10 ng/ml. Doses below 100 mg and once daily regimens were found to be inadequate in achieving the desired ‘target’ serum progesterone concentration.

Approximately 60 percent of the subjects treated with Endometrium[®] 100 mg twice daily or 200 mg twice daily had mid-to-late secretory transformation on an endometrial biopsy. In general, tissue (uterine) progesterone concentrations were higher with Endometrin[®] vaginal tablets compared to intramuscular progesterone (reference). However, higher tissue levels did not translate into achieving the desired secretory transformation of endometrium (62.5 % of subject achieved transformation with Endometrin[®] vs. 90 % with intramuscular progesterone).

In study 2005-08, the C_{avg} following multiple daily dosing of 100 mg twice daily, 100 mg three times daily and Crinone 8% gel 90 mg daily were 17.68 ± 5.66 , 23.8 ± 5.8 , and 13.92 ± 6.26 ng/ml, respectively. In this study, both 100 mg twice daily and three times daily regimens of Endometrin[®] resulted in steady state C_{max} , C_{avg} and C_{min} concentrations that were at or above the desired 10 ng/ml “target” concentration, with the three times daily regimen demonstrating higher concentrations of the two regimens. Compared to the results of the earlier PK/PD Study 2004-01, the single dose and steady-state serum progesterone exposures for the 100 mg twice daily regimen were higher in this study

(2005-08); the steady-state average serum progesterone concentrations (C_{avg}) were 7.4 ng/ml vs. 13.26 ng/ml in 2004-01 vs. 2005-08. Contribution from endogenous progesterone production in study 2005-08 due to the absence of Lupron pretreatment can not be ruled out.

The Division of Clinical Pharmacology III, Office of Clinical Pharmacology finds the clinical pharmacology data submitted in the application to be acceptable. (See Clinical Pharmacology Review for NDA 22-0057/S-000).

Pre-Clinical Pharmacology and Toxicology

The non-clinical toxicology of progesterone is well understood. Because progesterone has been well studied in animals and humans, and its effects are considered general knowledge, no new repeat-dose toxicity, genotoxicity, carcinogenicity, or reproductive and developmental nonclinical studies were submitted and none were required.

Nonclinical testing of Endometrin[®] focused on determining whether there was any new toxicity by the vaginal route of administration. The sponsor submitted two repeat-dose studies to examine vaginal irritation. Endometrin[®] was found to have minimal or no significant toxicity in either of these studies. In addition, dermal irritation and dermal sensitization were evaluated in rabbits and guinea pigs, respectively. Endometrin[®] was rated to be a nonirritant and a non-sensitizer.

There are no new nonclinical safety issues relevant to clinical use. From a Pharmacology-Toxicology viewpoint approval is recommended for NDA 22-057 for Endometrin 100 mg twice daily and 100 mg three times daily. (See Pharmacology/Toxicology Review for NDA 22-057/S-000).

Chemistry, Manufacturing and Controls (CMC):

┌
└ progesterone is micronized with a limit of 1 μm = NMT. All
drug substance information is provided by reference to DMF. ┌
└ A LOA was provided dated April 20, 2004

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The drug product is white to off-white, modified-caplet shaped vaginal insert debossed with "FPI" on one side and "100" on the other side. It is an immediate release tablet and is available in 100 mg strength. The tablets are packaged in aluminum/aluminum peel blisters. A disposable insertion device is copackaged with the product to facilitate insertion of the tablets into the vagina. Excipients corresponding to conventional oral tablets are used for the drug product. Adipic acid and sodium bicarbonate are used to

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┌
└ Some of the excipients such as lactose monohydrate and
pregelatinized starch. ┌

microbial test limit during stability to be the same as at the release. This response was deemed to be satisfactory. From a Microbiology standpoint the NDA is recommended for approval.

Product Name

The established name of the drug substance is progesterone (pregn-4-ene-3,20dione). The Office of Drug Safety (ODS) was consulted on August 28, 2006 to review the requested Tradename, Endometrin®. Per the Office of Drug Safety, the following recommendations were provided on February 16, 2007:

1. DMETS has no objections to the use of the proprietary name, Endometrin. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends consulting Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), for the proper designation of the established name.
3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
4. DDMAC finds the proprietary name Endometrin acceptable from a promotional perspective.

The result of the second consult to DMETS on the proprietary name was the same. The name is acceptable

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Conclusions and Recommendations

Progesterone products have been used since the 1980's as part of the in vitro fertilization treatment program to supplement the corpus luteum and support the luteal phase of the artificial cycle as well as an ensuing pregnancy, if this occurs. Prior to 1997, the main products used "off-label" for these purposes were progesterone in oil, administered intramuscularly, and micronized progesterone compounded as vaginal preparations. On May 13, 1997, Crinone[®] 8% (NDA 20-756) was Approved for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency.

With this application the Sponsor is seeking approval of two dosing regimens 100 mg twice daily and 100 mg three times daily of Endometrin[®] (progesterone) Vaginal Insert for the indication of pregnancy through progesterone supplementation as part of an Assisted Reproductive Technology treatment program for [redacted]. During drug development of this product several key recommendations were made by the Division to the Sponsor. These were:

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- The indication should emphasize pregnancy through the mechanism of luteal support
- Clinical pregnancy as defined by the presence of a gestational sac and fetal heartbeat should be the primary endpoint for an indication of pregnancy through luteal supplementation
- The study should be conducted as a double blind, double dummy designed trial. If a double-blind design is logistically not possible, then at a minimum the investigator and ultrasonographer should be blinded
- The primary efficacy analysis should be a two-sided 95% or one sided 97.5% confidence interval between the rates of clinical pregnancy obtained with Endometrin[®] and an approved active comparator
- Even though the Division believes that a non-inferiority limit to the lower bounds of the 95% confidence interval of the difference between Endometrin[®] and comparator should be 6 to 8%, the Division accepts a non-inferiority limit for the inferiority analysis consistent with a 10% non-inferiority limit on pregnancy rate accepted for the approval of Menopur[®]
- Randomization should be stratified by age and ovarian reserve and the analyses should be stratified and powered to show a difference for these subgroups.

The Sponsor essentially followed the Division's recommendation with respect to the indication, the primary endpoint of interest, the non-inferiority design with comparison to an active comparator and the non-inferiority limit to the lower bounds of the 95% confidence interval of the difference between Endometrin[®] and comparator. However, the Sponsor failed to follow the Division's recommendation on blinding of the trial and on stratifying and powering the study to show efficacy differences in the sub-group analyses. The Division felt that the double-blind or at least an investigator-blind design was necessary to minimize the introduction of investigator/physician biases at any of the multiple steps of decision making that occur during an in-vitro fertilization treatment cycle. Randomization after oocyte-retrieval certainly provides for fewer steps for the

introduction of investigator bias than would be the case with randomization at the start of the cycle, but nevertheless the opportunity to inappropriately influence the outcome still exists. A double-blind trial design as recommended by a 2003 Reproductive Health Advisory Committee, minimizes the opportunity to purposely manipulate the outcome of the trial.

The female infertility patient's age and ovarian reserve status (as measured by serum FSH level) are two critically important factors in determining the outcome of ovulation induction and in vitro fertilization/embryo transfer. Women of advanced reproductive age (greater than equal to 35 years of age) and poor ovarian reserve represent a different patient population from that of women under age 35 who undergo these procedures. Studies have generally suggested that basal FSH is an even better predictor than age of the outcome of in vitro fertilization. Women greater or equal to 35 years of age comprise an ever increasing proportion of women undergoing in vitro fertilization/embryo-transfer in the U.S. According to the 2004 Assisted Reproductive Technology Success Rates – National Summary and Fertility Clinic Reports published in 2006 by the Centers For Disease Control And Prevention, approximately 60% of all Assisted Reproductive Technology procedures are in women 35 years of age and older. Taking these statistics into account, it is incumbent that the Agency obtains efficacy and safety data in this age sub-group of ovulation induction and in vitro fertilization/embryo transfer –treated subjects before drug products go to market. To that end, the Division has been advising Sponsors since 2003 that their ovulation induction and in vitro fertilization/embryo transfer trials should be stratified at randomization and the analyses should be stratified and powered to demonstrate true differences, if they exist. This advice was given on multiple occasions to the Sponsor of Endometrin[®]. The Sponsor stratified randomization using an electronic system at baseline. However, the Sponsor failed to power the study sufficiently so that definitive statistical analyses result could be obtained on sub-groups.

The primary efficacy analyses demonstrated that Endometrin[®] 100 mg twice daily and 100 mg three times daily were non-inferior to Crinone[®] 8%. Thus efficacy was established in the ITT population. The safety profile was acceptable and non-concerning. Based on the efficacy and safety findings in the overall study population, I concur with the primary clinical and statistical reviewers and recommend approval of both the 100 mg twice daily dosing regimen and the 100 mg three times daily dosing regimen of Endometrin to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. However, the marketed label must clearly present the sub-group analyses so that patient and prescriber are fully informed regarding the results of the ongoing pregnancy rates by age and ovarian reserve as presented in Study 2004-02. Labeling negotiations have now been completed. The Division's labeling recommendations have been sent to and accepted by Ferring Pharmaceutical. See label dated June 20, 2007, which is attached to this review and is to be included with the decisional letter. This label appropriately advises prescriber and consumer on efficacy, safety and dosing of Endometrin[®] in patients less than 35 years of age and those 35 years of age and older.

Because Study 2004-02 was not appropriately powered to provide definitive efficacy results and because there is the question of whether or not some of the age subgroups would have demonstrated efficacy had the study been appropriately powered, I recommend that the Sponsor clarify these issues with a Phase 4 study to establish efficacy, the appropriate dosing regimen and safety in women greater than or equal to age 35 up to age 45. The clinical study should be designed as a non-inferiority comparison to Crinone[®] 8%/Prochieve[®]. Other details of the study should be discussed with and agreed upon by the Agency before the study is initiated.

Shelley R. Slaughter, MD., PhD
Medical Officer Team Leader and
Group Leader for NDA 22057

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

/s/

Shelley Slaughter
6/21/2007 05:12:13 PM
MEDICAL OFFICER

Scott Monroe
6/21/2007 05:18:53 PM
MEDICAL OFFICER

I concur with Dr. Slaughter's conclusions and recommendations.

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-057
Submission Code	S-000
Letter Date	August 21, 2006
Stamp Date	August 21, 2006
PDUFA Goal Date	June 21, 2007
Reviewer Name	Audrey Gassman, M.D.
Review Completion Date	June 20, 2007
Established Name	(progesterone) Vaginal Insert
(Proposed) Trade Name	Endometrin® Vaginal Inserts
Therapeutic Class	Progesterone
Sponsor	Ferring Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Insert
Dosing Regime	Administered vaginally as a 100 mg insert two or three times daily.
Indication	To support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women.
Intended Population	Infertile women undergoing ART procedures

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luteal supplementation. There are also other available drug products that can be used "off-label" for luteal supplementation though these are not specifically approved for this indication. These products include progesterone in oil administered intramuscularly and oral micronized progesterone.

The drug product Endometrin® was licensed from Biosoma, Ltd., which holds an Israeli patent for the product. A final formula identical to the original Israeli formula was selected for scale up and clinical supplies. Endometrin® is an approved product that has been marketed for luteal support in assisted reproduction in Israel and Hong Kong since 2003.

Endometrin® is an insert containing 100 mg of micronized progesterone and is applied intravaginally. The active drug substance, progesterone, is in a base containing lactose monohydrate, polyvinylpyrrolidone, adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized starch, and colloidal silicone dioxide. The product uses the adipic acid and sodium bicarbonate T A polyethylene applicator will be supplied with each vaginal insert, so that the applicators are not reused.

b(4)

The Sponsor (Ferring Pharmaceuticals, Inc.) is proposing to supply Endometrin® (progesterone) in aluminum/aluminum peel blisters that will pack the inserts individually in a foil pouch. These pouches will be available in cartons packed with 21 — vaginal inserts. A disposable vaginal applicator will be supplied for each insert in the pouch.

b(4)

The Sponsor began clinical development for Endometrin® with a pre-IND meeting held with the Division on October 23, 2003. The Sponsor subsequently submitted a phase 1 protocol and Study 2004-02 for review (Letter Date May 14, 2004). Clinical reviewer's comments on Study Protocol 2004-02 were sent in an Advice letter to the Sponsor on October 22, 2004. An End-of-Phase (EOP) 2 meeting was then held on February 28, 2005 to discuss preliminary results of the pharmacokinetic study (2004-01) and additional study design and statistical issues for Study 2004-02.

The Sponsor submitted a revised protocol and statistical analysis plan for Study 2004-02 in Amendment 023 and 024 (dated April 25, 2005 and June 24, 2005). Additional clinical and statistical comments on the revised phase 3 protocol for Study 2004-02 were relayed at the February 2005 EOP2 meeting and in an Advice letter dated September 12, 2005.

A pre-NDA meeting was held on 31-May-06. At this meeting, the Sponsor informed the Division of their plans to submit the results of a PK/PD study (2004-01) and one phase 3 clinical study (2004-02) to support the filing of the NDA.

Study 2004-02, a phase 3, open-label (only the ultrasonographer who was not involved in decision making was blinded), 10-week, active-controlled clinical trial, was conducted to provide the primary safety and efficacy data in support of Endometrin®. Despite the Agency's recommendation that any decision maker be blinded to treatment to minimize bias, the sponsor chose only to blind the ultrasonographer and not the investigator. Two phase 1 studies were conducted at request of the Agency and are submitted with the application. Study 2004-01 was a

dose-ranging pharmacokinetic study to evaluate three dosages and two dosage regimens of Endometrin® on endometrial development and determine the onset of steady-state. Study 2005-08 was a phase 1 pharmacokinetic study to evaluate the pharmacologic parameters of two dose regimens of Endometrin®.

The Sponsor is seeking approval of two dosage regimens of 100 mg progesterone inserts (100 mg twice daily and 100 mg three times daily) for the indication of pregnancy through progesterone supplementation as part of an (ART) treatment program for _____ women.

b(4)

1.3.2 Efficacy

Phase 3 Study 2004-02 was a multi-center, randomized, open-label, phase 3 study in which a total of 1211 healthy infertile women were randomized at 25 clinical sites to one of three treatment groups in a 1:1:1 ratio:

- 100 mg of Endometrin® twice daily
- 100 mg of Endometrin® three times daily
- 8% Crinone® gel (90 mg of progesterone) once daily

The primary objective of the final amended Study 2004-02 was to determine the efficacy of Endometrin® administered vaginally in terms of ongoing pregnancy rates in women undergoing in vitro fertilization. The primary efficacy analysis was pre-specified as a non-inferiority (within 10%) comparison to 8% Crinone® gel

The study design for Study 2004-02 complied with the recommendations made in the Division's Advice letters (Letter dates October 22, 2004 and September 12, 2005, respectively), and also at the February 2005 EOP 2 meeting. The first patient visit occurred on July 18, 2005 and the last patient visit occurred on April 11, 2006 for a total study duration of approximately 9 months.

A total of 1504 patients were screened, of whom 155 subjects were screening failures. Of the 1349 subjects that began GnRH agonist down-regulation, 27 were down-regulation failures, resulting in a total of 1322 subjects undergoing ovarian stimulation with gonadotropins. 111 subjects were gonadotropin stimulation failures, or did not complete their gonadotropin cycle for other reasons.

Study 2004-02 had 1211 subjects that were randomized at oocyte retrieval to treatment (m-ITT population who completed gonadotropin down-regulation and ovarian stimulation). Of the 1211 subjects: 404 subjects were randomized to Endometrin® twice daily, 404 subjects to Endometrin® TID and 403 to Crinone® 8%. Of the 1211 subjects, 36 (3%) failed to have embryo transfer. The most common reasons for failure to complete the study after randomization included: no positive pregnancy test at Visit 3 or 4 (548 of 1211 subjects or 45.3%), biochemical or gestational sac only (72 of 1211 subjects or 5.9%) and loss of pregnancy through ectopic/abortion/miscarriage (36 of 1211 or 3.0%). All randomized 1211 subjects received Endometrin® or Crinone® 8% and were (according to the protocol), evaluable for safety and efficacy.

No patients were enrolled under the original protocol. Protocol Amendment 1, dated June 17, 2005 (prior to the start of subject enrollment on July 18, 2005), extended the window of randomization from one day to two days, increased the window for Study Visits 3 and 5A to 5 days, modified the inclusion/exclusion criteria, and allowed assisted hatching and intracytoplasmic injection procedures.

The final protocol (Protocol Amendment 2) was dated January 13, 2006 after the start of subject enrollment. This Amendment clarified that at least 990 subjects would be enrolled, with at least 330 per treatment group, and also increased the cap for study center enrollment from 100 to 150.

Reviewer's comment: The final protocol in Amendment 023 was reviewed by the Statistical Division, but not the Clinical Review Division.

In addition, Amendment 023 added an evaluation of the per protocol population in addition to the primary evaluation of the ITT population (all randomized subjects who took at least one dose of study medication) and the efficacy population (all randomized subjects who underwent an embryo transfer). This additional study population was defined as including all subjects that were in the efficacy population without major protocol violations and who didn't take any additional medications for luteal support that would influence the luteal phase. An addendum to study 2004-02 was added on November 21, 2005 to allow two of the 25 investigator sites to undergo additional blood measurements of hormones including estrogen and progesterone and additional transvaginal ultrasounds during treatment in up to 30 subjects already participating in study 2004-02 (5-10 per treatment group).

The primary efficacy endpoint for Study 2004-02 was ongoing pregnancy (defined as identification of fetal heart movement at approximately 6 weeks of gestation).

The ITT group (subjects that completed screening, down-regulation, ovarian stimulation, egg retrieval and then were randomized on day of or day following retrieval) was used for evaluation of the Endometrin®. The primary endpoint (ongoing pregnancy) across the treatment groups was analyzed using a two-sided 95% confidence interval with a pre-specified non-inferiority margin of 10%. No adjustment for multiple comparisons was required as a step-down procedure was used to compare ongoing pregnancy rates between Endometrin® groups and Crinone®. If non-inferiority (10% lower boundary relative to Crinone®) was substantiated for the comparison of Endometrin® 100 mg three times daily to Crinone®, then the non-inferiority analysis of the pregnancy rate for Endometrin® twice daily vs. Crinone® was performed. The results of Study 2004-02 for the ITT population are shown in Table 1:

**Appears This Way
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Table 1: Ongoing pregnancy rate per retrieval for the ITT population

	Endometrin® 100mg BID	Endometrin® 100 mg TID	Crinone® 8% Once Daily
Number of subjects	404	404	403
Ongoing pregnancy rate n (%)	156 (39%)	171 (42%)	170 (42%)
95% Confidence Interval (CI)	[33.8,43.6]	[37.5,47.3]	[37.3,47.2]
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	-3.6% [-10.3]	0.1% [-6.7]	

Source: Adapted from NDA 22-057/S-000, Final Report, Table 15, page 62 of 7469.

Based on these clinical pregnancy rates:

- The 100 mg Endometrin® three times daily dosing regimen was determined to be effective as the difference between Endometrin® (three times daily) and Crinone® was within the 10% lower bound [95% Confidence Interval lower bound difference = -6.7].
- The 100 mg Endometrin® twice daily dosing regimen was determined to be effective as the difference between Endometrin® (twice daily) and Crinone® was at the 10% lower bound [95% Confidence Interval lower bound difference = -10.3%]

Reviewer's comment: It is important to note that these pregnancy rates are per retrieval, not per cycle as these subjects were not randomized until day of oocyte retrieval. Pregnancies per retrieval are slightly higher than per cycle as the denominator is lower per retrieval. Pregnancy outcomes in this review are listed as per retrieval to prevent inaccurate comparisons to pregnancy outcome data in other studies and reports that may use a different denominator.

Subjects in Study 2004-02 were stratified by subject age and level of follicular stimulating hormone (ovarian reserve) as recommended by the Division in an Advice letter dated October 22, 2004. However, the stratification selected was based on matching the Society for Assisted Reproductive Technology database (SART 2002) data. The ongoing pregnancy rate results stratified by age and ovarian reserve are shown in Table 2:

**Appears This Way
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Table 2: Sponsor's ongoing pregnancy rate in age and ovarian reserve defined subgroups

Ongoing pregnancy per retrieval	Endometrin® 100mg BID (ITT N=404)	Endometrin® 100 mg TID (ITT N=404)	Crinone® 8% once daily (ITT N=403)
Subjects < 35 years old (N)	247	247	243
Ongoing pregnancy rate n (%)	111 (44.9%)	117 (47.4%)	108 (44.4%)
95% Confidence Interval (CI)	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference between Endometrin® and Crinone®	0.5%	2.9%	
95% CI lower bound for difference	[-8.3%]	[-5.9]	
Subjects 35 – 37 years old (N)	89	93	98
Ongoing pregnancy rate n (%)	27 (30.3%)	37 (39.8%)	41 (41.8%)
95% Confidence Interval (CI)	[21.0, 41.0]	[29.8, 50.5]	[31.9, 52.2]
Difference between Endometrin® and Crinone®	-11.5%	-2.1%	
95% CI lower bound for difference	[-25.2]	[-16.0]	
Subjects 38-40 years old (N)	55	46	53
Ongoing pregnancy rate n (%)	16 (29.1%)	12 (26.1%)	16 (30.2%)
95% Confidence Interval (CI)	[17.6, 42.9]	[14.3, 41.1]	[18.3, 44.3]
Difference between Endometrin® and Crinone®	-1.1%	-4.1%	
95% CI lower bound for difference	[-18.3]	[-21.8]	
Subjects 41-42 years old (N)	13	18	9
Ongoing pregnancy rate n (%)	2 (15.4%)	5 (27.8%)	5 (55.6%)
95% Confidence Interval (CI)	[1.9, 45.4]	[9.7, 53.5]	[21.2, 86.3]
Difference between Endometrin® and Crinone®	-40.2%	-27.8%	
95% CI lower bound for difference	[-78.1]	[-66.3]	
Subjects with FSH < 10 IU/L (N)	350	347	350
Ongoing pregnancy rate n (%)	140 (40.0%)	150 (43.2%)	147 (42.0)
95% Confidence Interval (CI)	[34.8, 45.3]	[37.9, 48.6]	[36.8, 47.4]
Difference with Crinone®	-2.0%	1.2%	
[95% CI lower bound]	[-9.3]	[-6.1]	
Subjects with FSH 10-15 IU/L (N)	46	51	49
Ongoing pregnancy rate n (%)	16 (34.8%)	20 (39.2%)	23(46.9%)
95% Confidence Interval (CI)	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
Difference with Crinone®	-12.2%	-7.7%	
[95% CI lower bound]	[-31.8]	[-27.1]	

Source: Adapted from NDA 22-057/S-000, Final Report, Adapted from Table 17, page 65 and Table 14.2.2.2, page 190 of 7469.

Reviewer's comment: The Sponsor chose the age subgroups based on matching the stratification to that performed for the Society for Assisted Reproductive Technology database (SART 2002) data. The number of subjects was small in each sub-group of women 35 years of age and greater, as well as in the sub-groups defined by ovarian reserve (serum FSH between 10 and 15 IU/L). The sponsor failed to take the Agency's advice to appropriately power the age and FSH sub-group analyses, provided at the EOP 2 meeting (28-Feb-05) and again in a subsequent advice letter (dated 21-Jan-05).

The Agency did additional subgroup analyses looking at subjects grouped as younger than 35 years of age and those grouped as 35 years of age or greater (and not by 2 to 3 year increments as the sponsor had done) in order to increase the numbers of subjects in the 35 and older group. The Division's analyses are shown in Table 3:

Table 3: Ongoing pregnancy in age and ovarian reserve defined subgroups (Division's)

Ongoing pregnancy per retrieval	Endometrin® 100 mg BID N=404	Endometrin 100 mg TID N=404	Crinone® 8% once daily N=403
Subjects < 35 years of age (N)	247	247	243
Ongoing pregnancy rate n (%)	111 (44.9%)	117 (47.3%)	108 (44.4%)
95% Confidence Interval (CI)	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference with Crinone®	0.5%	2.9%	--
[95% CI for difference]	[-8.3, 9.3]	[-5.9, 11.7]	--
Subjects 35-42 years of age (N)	157	157	160
Ongoing pregnancy rate n (%)	45 (28.7%)	54 (34.4%)	62 (38.8%)
95% Confidence Interval (CI)	[21.7, 36.4]	[27.0, 42.4]	[31.2, 46.8]
Difference with Crinone®	-10.1%	-4.4%	--
[95% CI for difference]	[-20.3, 0.3]	[-14.9, 6.3]	--
Subjects with FSH < 10 IU/L (N)	350	347	350
Ongoing pregnancy rate n (%)	140 (40.0%)	150 (43.2%)	147 (42.0)
95% Confidence Interval (CI)	[34.8, 45.3]	[37.9, 48.6]	[36.9, 47.4]
Difference with Crinone®	-2.0%	1.2%	--
[95% CI for difference]	[-9.3]	[-6.1]	--
Subjects FSH 10-15 IU/L (N)	46	51	49
Ongoing pregnancy rate n (%)	16 (34.8%)	20 (39.2%)	23 (46.9%)
95% Confidence Interval (CI)	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
Difference with Crinone®	-12.2%	-7.7%	--
[95% CI for difference]	[-31.0, 7.7]	[-26.6, 11.6]	--

Source: Adapted from NDA 22-057/S-000, Final Report, Adapted from Table 17, page 65 and Table 14.2.2.2, page 190 of 7469.

Reviewer's comments:

- *The efficacy information for this study was collected only at the 6 week post-embryo transfer time point and not up to the 10 weeks of total progesterone exposure. Only safety information was collected after the final ultrasound at approximately 6 weeks time.*
- *The ongoing pregnancy rates for subjects with normal ovarian reserve (serum FSH < 10 IU/L) and subjects under 35 years of age in both Endometrin® treatment regimes are non-inferior (defined by a 10% non-inferiority limit to the lower bounds of the 95% confidence interval) to the ongoing pregnancy rates for the same subgroups of subjects treated with Crinone®.*
- *The ongoing pregnancy rates for subjects over 35 and/or for those with poor ovarian reserve receiving Endometrin® twice daily and three times daily treatment regimens appears to be inferior compared to Crinone®. The reviewer notes that the study was not powered (contrary to the recommendations of the Agency) to show a difference in the subgroup population. Perhaps the outcome might have been different with appropriately powered subgroup analyses. Clinically, the decreased pregnancy rate in these older (35 and older sub-groups) subjects is concerning.*

1.3.3 Safety

Progesterone, either given alone or in combination with an estradiol preparation, has been used clinically off-label for luteal support after Assisted Reproductive Technology procedures since the first successful pregnancy from in vitro fertilization occurred in 1978.

The safety database presented in this submission for 100 mg of vaginal progesterone consisted of 884 total subjects treated in three clinical studies. These studies included:

- One phase 3 active-controlled clinical study (2004-02)
- Two phase 1 clinical studies (2004-01 and 2005-08)

Phase 3 Study 2004-02, which provided the primary safety database, used the to-be-marketed formulation of Endometrin® and included 808 subjects who received one of two dosing regimens of Endometrin® (100 mg three times daily or 100 mg twice daily).

The two phase 1 Studies (2004-01 and 2005-08), which evaluated a total of 76 subjects (60 healthy pre-menopausal female subjects that used Endometrin®), also provided additional limited safety information with short-term use (10 days of treatment or less). These two studies were both conducted with the proposed to-be-marketed formulation of Endometrin® (progesterone vaginal insert).

There were no new safety signals or trends (i.e. events that have not been previously reported for other progesterone products used for luteal supplementation) seen for either dosing regimen (100 mg progesterone vaginal inserts twice daily or three times daily) in Study 2004-02.. There were no clinically significant differences between treatment groups in the number of subjects who completed Study 2004-02 and in the reasons for

discontinuation. No deaths occurred during or following the conduct of phase 3 Study 2004-02 or the two phase 1 Studies (2004-01 and 2005-08) that used the to-be-marketed Endometrin® formulation (progesterone vaginal inserts).

Safety findings for the primary Study 2004-02 included:

1. Serious adverse events requiring hospitalization occurred in 31 subjects (14 subjects of 404 [3%] in the 100 mg twice daily Endometrin® group, 8 subjects of 404 [2%] in the 100 mg three times daily Endometrin® group, and 9 subjects of 403 [2%] in the Crinone® 8% group. All of these serious adverse events resolved, and three of these events resulted in discontinuation of Endometrin® (ovarian torsion [subject 09012] in the Endometrin® twice daily group, severe ovarian hyperstimulation [subject 11007] in the Endometrin® three times daily group, and moderate ovarian hyperstimulation [subject 17030] in the Endometrin® three times daily group).
2. None of the three serious adverse events that resulted in discontinuation were determined to be related to Endometrin® or Crinone® treatment by the Sponsor.
3. A total of 1492 adverse events were reported in 642 of 1211 subjects in the three progesterone treatment groups overall.
 - The more common TEAEs in the Endometrin® twice daily treatment group included: Post-ovocyte retrieval pain in (115 of 404 subjects [28%]), abdominal pain (43 of 404 subjects [11%]), nausea (32 of 404 subjects [8%]) and ovarian hyperstimulation syndrome (30 of 404 subjects [7%]).
 - The more common TEAEs in the Endometrin® three times daily treatment group included: Post-procedure pain in (102 of 404 subjects [25%]), abdominal pain (45 of 404 subjects [11%]), nausea (29 of 404 subjects [7%]) and ovarian hyperstimulation syndrome (27 of 404 subjects [7%]).
4. Vaginal hemorrhage was reported in a total of 32 subjects [2.6%] in the three treatment groups (7 of 404 subjects [2%] in the Endometrin® twice daily group, 9 of 404 subjects [2%] in the Endometrin® three times daily group and 16 of 403 subjects [4%] in the Crinone® group).
5. Subject discontinuation:
 - Discontinuations from treatment were reported in 58.6% of randomized subjects (771 of 1211 total subjects in the three progesterone treatment groups). The majority of discontinuations (47.9%) were a result of a negative pregnancy test at Visit 3 or 4 (548 of 1211 in the three treatment groups).
 - Discontinuation as a result of an adverse event occurred in 0.8% (10 of 1211 total subjects) in the three progesterone treatment groups. Nine of the ten discontinuations occurred in the Endometrin® treatment groups:
 - Two [2 of 404 subjects] in the Endometrin® twice daily group (0.2%)
 - Seven [7 of 404 subjects] in the Endometrin® three times daily group (1.7%), compared to
 - One [1 of 403 subjects] in the Crinone® treatment group (0.2%).

In Study 2004-02, overall treatment-related adverse event (AEs) appeared clinically similar when comparing the twice daily and three times daily groups (215 of 404 subjects [53.2%] with at least one AE in the Endometrin® twice daily group compared to 217 of 404 subjects [53.7%] with at least one AE in the Endometrin® three times daily group. In addition, overall treatment related adverse events appeared similar between the two Endometrin® treatment groups (53.2% and 53.7% in the twice daily and three times daily groups, respectively) and Crinone® (210 subjects with at least one AE of 403 subjects [52.1%]) in terms of overall treatment-related AEs.

Reviewer's comments:

- 1. Exposure and total safety data for study groups were collected up to 10-weeks post-embryo transfer*
- 2. There does not appear any difference between the Endometrin® treatment groups in either serious adverse events or overall adverse events (including vaginal hemorrhage and vaginal irritation) that would lead to concerns of a new trend of dose-dependent adverse events compared to Crinone®.*
- 3. There were more discontinuations in the Endometrin® three times daily group for rash or urticaria (3 subjects) compared to none in the Endometrin® twice daily and Crinone® groups. The reviewer does note that these discontinuations were relatively infrequent (<1%), and not life-threatening. This reviewer has concerns that once Endometrin® is in general use, there may be a greater percentage of allergic reactions than those seen in the clinical study. Therefore, the Division should be diligent in monitoring AERS database for a signal regarding the rate of allergic reactions during the post-marketing period*

The two phase 1 studies (2004-01 and 2005-08) treated a total of 76 subjects. In these subjects:

1. No subjects died or developed serious adverse events during the conduct of the two pharmacokinetic studies.
2. In the two phase 1 studies, 31 subjects experienced treatment-emergent adverse events. In Study 2005-08, 5 subjects of 18 [27.8%] had at least one adverse event with Endometrin® use. In Study 2004-01, 19 subjects of 58 [32.8%] had at least one adverse event with Endometrin® use. The more common TEAEs in the two phase 1 clinical studies included: headache (4 subjects in Study 2004-01), dysmenorrhea (4 Subjects in Study 2004-01), nausea (3 subjects in Study 2004-01) and vaginal haemorrhage (3 subjects in Study 2005-08).
3. Subject discontinuation: In the two phase 1 studies two (2) subjects of 58 [3.4%] were discontinued from Study 2004-01 due to an adverse event, although neither discontinuation was considered to be a result of Endometrin® therapy by the Investigators. The first discontinuation was subject 02058 who developed left calf pain during down-regulation with a gonadotropin-hormone releasing agonist 3 days prior to Endometrin® therapy. After receiving the first dose of Endometrin®, the subject was prematurely discontinued from treatment for this calf pain. The calf pain resolved without additional pregnancy treatment. A second discontinuation was subject 02027 who had a positive pregnancy test on Day 33 after receiving

gonadotropin-hormone releasing agonist prior to being assigned to a progesterone dose-treatment group and was discontinued from treatment. No subjects were discontinued from Study 2005-08 during study treatment.

1.3.4 Dosing Regimen and Administration

One other progesterone product is approved for luteal supplementation after Assisted Reproductive Technology procedures (Crinone® 8%) in a once daily regime). Injectable progesterone products in oil are used off-label for this indication and are also usually administered daily. In the primary safety and efficacy clinical trial (Study 2004-02), subjects either applied:

- A 100 mg Endometrin® inserts administered vaginally at the same time each morning and evening for 10 weeks with a single use plastic applicator (first dose administered the day after oocyte retrieval)
- A 100 mg Endometrin® inserts administered vaginally at the same time each morning, afternoon, and evening for 10 weeks with a single use plastic applicator (first dose administered the day after oocyte retrieval)
- Crinone® 8% gel inserted vaginally in the evening for 10 weeks with a single use disposable polyethylene applicator (first dose administered the day after oocyte retrieval)

These instructions for Endometrin® will be reflected in labeling.

Reviewer's comment: This reviewer has significant concerns based on the current available efficacy data; there is insufficient support for Endometrin use in the 35 and older population group. The information seen in the sub-group analyses, although the study was not appropriately powered, should be addressed in labeling as this reviewer believes it is important for both prescribers and patients to know.

1.3.5 Drug-Drug Interactions

There are no reports or studies documenting that drugs that inhibit CYP 3A4 or other CYP-P450 isoforms increase plasma levels of progesterone. The clinical relevance of an effect of progesterone on the metabolism of concomitant medication is low, as published literature suggests that progesterone does not inhibit cytochromes involved in the metabolism of most drugs. There were no other clinical issues in the studies or the published literature that raise concerns that additional drug-drug interaction testing needs to be performed for Endometrin®.

1.3.6 Special Populations

Endometrin® Vaginal Insert for vaginal administration was investigated in infertile premenopausal women. Ages ranged from 19 to 42 years with a mean age of 33 years in all

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{Audrey Gassman, MD}
{NDA 22-057/S-000}
{Progesterone vaginal insert}

treatment groups. No pharmacokinetic studies were conducted in special populations, including women with renal or hepatic impairment.

Clinical studies involving males and children are not warranted as progesterone supplementation is not indicated in these populations.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Endometrin® (progesterone) Vaginal Insert is a vaginally applied drug product that contains progesterone as the active ingredient. Endometrin® is supplied in aluminum blister packages. A commercially available plastic insertion device is provided for each insert to facilitate vaginal use. The proposed drug product Endometrin® for marketing includes the following inactive ingredients: colloidal silicone dioxide NF, lactose monohydrate NF, pregelatinized starch NF, polyvinylpyrrolidone USP, adipic acid FCC, sodium bicarbonate USP, sodium lauryl sulfate NF, magnesium stearate NF, and _____ . Adipic acid and bicarbonate _____ and pregelatinized starch is _____ . The Sponsor is seeking approval for two dosage regimes of Endometrin®: 100 mg of Endometrin® twice daily and 100 mg of Endometrin® three times daily (200 mg of progesterone and 300 mg of progesterone, respectively).

b(4)

The established name of the drug substance is progesterone (pregn-4-ene-3,20dione). The Office of Drug Safety was consulted on August 28, 2006 to review the requested Tradename, Endometrin®. Per the Office of Drug Safety, the following recommendations were provided on February 16, 2007:

1. DMETS has no objections to the use of the proprietary name, Endometrin. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends consulting Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), for the proper designation of the established name.
3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
4. DDMAC finds the proprietary name Endometrin acceptable from a promotional perspective.

Reviewer's comment: DMETS requested that their labeling comments be conveyed to the Sponsor, pending NDA 22-057/S-000 regulatory action. Their labeling comments were incorporated into the label sent to the Sponsor as outlined in section 10.2 of this review.

The pharmacologic class of this product is that of progesterone.

The Sponsor's proposed indication for Endometrin® is Pregnancy through progesterone supplementation as part of an (ART) treatment program for _____

b(4)

Reviewer's comment: The Clinical Review team recommended the following revised indication, "Endometrin® is a progesterone indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women" to better define the indication.

Two dosing regimens were included in the primary 10-week safety and effectiveness clinical trial: 1) 100 mg Endometrin® inserts applied vaginally twice daily and 2) 100 mg Endometrin® inserts applied vaginally three times daily. Infertile women undergoing Assisted Reproductive Technology procedures, aged 18 to 42 years and older, inclusive, were eligible to participate in the primary safety and efficacy clinical trial.

The Chemistry reviewer identified four microbiology issues that needed to be addressed for Endometrin® (NDA 22-057/S-000) in a consult dated October 3, 2006):

- Whether the established microbial limits for Endometrin® were acceptable.
- Whether Microbial Limits Testing should be included at stability
- Whether the Limits for Water needed to be tightened
- Whether the packaging line needed to be treated prior to manufacturing.

The Product Quality reviewer for Microbiology in an Email dated February 5, 2007 stated that after a preliminary review of the submission, reported that there was a lack of microbial limits at stability time points, particularly with the moisture limits for Endometrin® inserts set at _____. From microbiological perspective, a few osmophilic yeast can grow at water activity levels of 0.60. Therefore, the microbiological reviewer recommended that the Sponsor should:

b(4)

1. Rigorously monitor the moisture limits of _____ and
2. Confirm that no microbial growth is promoted by performing microbial limits test at least at stability end point.

The Product Quality reviewer for Microbiology completed the review of Endometrin and determined that the application was approvable on condition that the Microbial Limits tests currently conducted at release must be performed at the Stability End Point (see review dated February 28, 2007). On May 24, 2007 the Sponsor committed to add the microbial tests would be conducted in the revised stability protocol with the microbial test limit during stability to be the same as release (see CMC review dated June 15, 2007).

The Chemistry and Manufacturing review team found the CMC information provided by the Sponsor acceptable pending a satisfactory cGMP recommendation from the Office of Compliance (Review dated June 15, 2007)

2.2 Currently Available Treatment for Indications

Recognition of the therapeutic potential of progesterone began in the 1930's with the extraction and purification of progesterone. The class of drugs "Progestogens" (which includes progesterone) was declared effective in the Federal Register Notice of October 10, 1973 for amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. NDAs were submitted for progesterone injection to comply with a Federal Register publication of September 9, 1971 to provide control data only. A determination was in a memorandum dated June 20, 1972 from the Director, Office of Scientific Evaluation to the Director, Division of Metabolic and Endocrine Drug Products that "preclinical and clinical trials are not necessary for progesterone injectables (as specified in the U.S.P monograph) for the two effective indications (amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology)".

Initial reports of successful clinical pregnancies resulting from the use of progesterone for luteal support after ovarian stimulation were first reported in the 1970's. In the 1980's, off-label use of progesterone intramuscular injection for luteal support post-embryo transfer was incorporated into the treatment regime for in vitro fertilization (IVF) in the United States. Clinical studies for the use of intramuscular injections of progesterone for luteal support in patients with complete and partial ovarian failure were initially published in the 1980s. The exogenous progesterone was presumed to prepare the endometrial lining to produce favorable histology for implantation.

There is currently one progesterone vaginal gel product (Crinone® - NDA 20-756) that is approved and marketed in the United States for progesterone supplementation as part of an Assisted Reproductive Technology program. Crinone® 8% vaginal gel (90 mg of progesterone daily) is applied once a day for the indication of progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency. This vaginal gel product was approved on May 13, 1997

2.3 Availability of Proposed Active Ingredient in the United States

Products containing progesterone have been used approved and used clinically for since it was synthesized in the late 1930s. The two most recent approved products containing progesterone include:

- Prometrium® (progesterone USP): Prometrium® is formulated in capsules that contain 100 mg or 200 mg of progesterone for oral administration. Prometrium® is approved for use in women who have secondary amenorrhea and for the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogen tablets. For prevention of endometrial hyperplasia, Prometrium® is administered to postmenopausal women as a single daily dose of 200 mg in the evening for 12 days sequentially per 28-day cycle. For patients with secondary amenorrhea it is administered as a single

daily dose of 400 mg (4 capsules) in the evening for 10 days. (Reference NDAs 19-781 and 20-843).

- Crinone® (progesterone gel): Crinone® is formulated in a bioadhesive vaginal gel that contains 45 mg or 90 mg of progesterone in a gel for vaginal administration. Crinone® 8% (once daily) is approved for progesterone supplementation or replacement as part of an Assisted Reproductive Technology treatment for infertility treatment for 10-12 weeks. Crinone® 4% and 8% are approved for treatment of secondary amenorrhea administered every other day for up to a total of six doses (Reference NDAs 20-701 and 20-756).

2.4 Important Issues With Pharmacologically Related Products

The most concerning serious adverse events associated with progesterone therapy can be grouped into adverse events as a result of the pharmacologic action of the drug (including severe allergic reactions) and adverse events as a result of drug administration (including vaginal inflammation from the excipients that result in the effervescence for Endometrin®). These two serious adverse event groups could potentially result in premature termination of treatment and consequently, adversely affect clinical pregnancy outcome.

Anaphylaxis, anaphylactoid reactions, and the discontinuation rate resulting from allergic reactions are the most concerning pharmacologic adverse events associated with progesterone use, probably as a result of the excipients used to dissolve progesterone. None of the patients in the pharmacokinetic studies discontinued because of allergic or anaphylactic reactions. In one of the pharmacokinetic studies (2005-08), one patient developed a rash, but was not discontinued from treatment. No episodes of anaphylaxis were reported in any progesterone treatment group in phase 3 Study 2004-02. However, three (3) patients discontinued Endometrin® therapy after developing a skin reaction to Endometrin® three times daily. These patients developed either a significant skin rash or urticaria. No subjects in the Endometrin® twice daily or Crinone® groups discontinued treatment for skin reactions.

Reviewer's comment: It is possible that these four patients with rash or urticaria had some form of mild allergic reaction to the Endometrin® three times daily application. Given the lack of severity of these reports, from a clinical perspective, this is acceptable to the clinical reviewer. In this reviewer's opinion, the possibility of allergic reactions to Endometrin® will need to be included in labeling and monitored during post-marketing of Endometrin®.

Vaginal irritation and discomfort were another safety concern associated with vaginal progesterone use. The discontinuation rate resulting from vaginal irritation is a concern for any vaginally inserted drug product. No subjects discontinued from any treatment groups in the pharmacokinetic studies (2004-01 or 2005-08) or the primary phase 3 Study 2004-02 for vaginal irritation or discomfort.

2.5 Presubmission Regulatory Activity

On October 23, 2003, the Division held a pre-IND meeting held with the Sponsor to review outlines of chemistry and manufacturing information, non-clinical toxicology study proposals, and outlines of proposed clinical protocols. At the October 23, 2003 meeting, the Division requested the Sponsor submit the completed clinical protocols for review.

On May 14, 2004, the Sponsor submitted the initial phase 3 protocol for Study 2004-02 entitled, "A Multi-Center, Randomized, Open-Label, Parallel-Group Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) in Female Patients Undergoing In Vitro Fertilization".

On October 22, 2004, an Advice letter was sent to the Sponsor with recommendations and comments on Study 2004-02. The Clinical comments in that October 2004 Advice letter included (verbatim):

1. We recommend that you use a progesterone product that is approved for assisted reproductive technologies (ART) as a comparator.
2. We recommend that you perform the study in a double-blind manner utilizing a double-dummy.
3. We recommend the primary endpoint be clinical pregnancy and be defined by the presence of a gestational sac and fetal heartbeat beginning at six weeks after human chorionic gonadotropin (hCG) has been administered to induce final follicular maturation.
4. We recommend the following secondary efficacy endpoints be evaluated:
 - Incidence of livebirth rate
 - Rate of spontaneous abortion
 - Rate of ectopic pregnancy
 - Cycle cancellation rate
 - Rate of vaginal hemorrhage
5. We recommend that the primary efficacy analysis be a two-sided 95% or one-sided 97.5% confidence interval analysis (C.I.) of the difference between the rates of clinical pregnancy obtained with Endometrin® versus a comparator. The lower bound of the confidence interval should exclude a difference greater than 6% in favor of the comparator.

On February 28, 2005, an End-of-Phase (EOP2) meeting was to discuss preliminary results of a completed pharmacokinetic study (2004-01) and to address study design and statistical issues for the phase 3 protocol (2004-02). Clinical comments from the Division (verbatim) included:

- 1) We remind you of our previous recommendations (Advice letter dated 22-Oct-04) regarding a proposed clinical trial with the primary endpoint of clinical pregnancy rate. Of these recommendations, the following were not addressed in the protocol contained in you briefing document:

- “The study investigator should be blinded to the treatment (assessor-blind). No individual who is making any decisions (investigator or ultrasonographer should be aware of treatment). We recommend using a clinical nurse and consulting safety gynecologist.
 - We recommend that you exclude subjects with a body mass index (BMI) > 38 kg/m²
 - We recommend you record detailed past obstetrical history including: gravidity, parity, previous abortions, and ectopic pregnancies.
 - We recommend that you provide a standard method (grading) of determining the severity of ovarian hyperstimulation syndrome (both in terms of what criteria would lead to cancellation and what would be considered a serious adverse event) to allow uniformity between sites.
- 2) You have proposed 2004-02 as a non-inferiority study comparing Endometrin® 100 mg BID and 200 mg BID (see previous comments on dosage) to Crinone® 8% gel. You have further proposed that based on an expected clinical pregnancy rate of 30% in the comparator, non-inferiority will be declared if the lower bound of the 95% confidence interval of the difference in clinical pregnancy rates between Endometrin® and Crinone® 8% excludes a difference greater than 15% in favor of Crinone® 8%.

We do not concur with your non-inferiority limit.

You mention that the subject sample size to accomplish our previously recommended non-inferiority limit of 6 % would be larger than that required for approval of the comparator Crinone® 8% (May 13, 1997) and other (infertility) drug products presented to the FDA. We do not dispute this. However, in September 2003 we received the Reproductive Health Advisory Committee's recommendation that we should look at the endpoint of clinical pregnancy in our evaluation of gonadotropin drug products used to help infertile women to conceive. This is a departure from the previous approval requirements for gonadotropins and requires a larger sample size. Even more recently on October 29, 2004, we granted approval of your drug product Menopur® administered by subcutaneous injection (NDA 21-663) based upon Study MFK/IVF/0399E (protocol not presented to the FDA for review) that evaluated a total of 727 subjects (373 in the Menopur® arm and 354 in the comparator arm) for the primary endpoint of clinical pregnancy rate. In this study, for which agreements were made prior to the Advisory Committee, the pre-specified non-inferiority limit (for which the lower-bound of the 95% confidence interval could not exceed) was a difference of 10%. The lower bound of the 95% confidence interval of the difference by your analysis was -3.3 thus excluding that the difference in pregnancy rate between Menopur® and the comparator was greater than 10% in favor of the comparator. The Division does not wish to lower the standard for demonstration of efficacy for Endometrin® relative to this recent (2004) approval of Menopur®.

The Division notes that at the September 29, 2003 Advisory Committee meeting, Dr. Emerson made some calculations on the lower acceptable limit of the 95% confidence interval of clinical pregnancy rate based on data from previously approved gonadotropin or menotropins drug products. The Division's clinical team interpreted this as a recommendation by Dr. Emerson that the difference between products should be no greater than this value of 6% (or 8%). We note that it is not entirely clear to us that this recommendation was tied only to an approximately 20% expected clinical pregnancy rate. We have sought clarification from Dr. Emerson regarding his calculations and whether these would be adjusted with a background rate of 30% as opposed to 20%.

Given all of the preceding information, we continue to recommend a tighter non-inferiority limit of 6%-8% on the difference in clinical pregnancy rate. Most importantly, we do not feel that the bar for efficacy demonstration of this product should be lower than for your recently approved Menopur® which represents an application that is close to our thinking on these drug products. Remember, that these are our recommendations (guidance) and represent our thoughts relative to demonstration of efficacy.

In view of the difference in interpretation of the recommendation in the Advisory Committee transcript, we would be willing to allow (i.e., before publication of a draft guidance), a pre-specified 10% difference as the lower limit of the 95% Confidence Interval such as in the Menopur® Study MFK/IVF/0399E.

Reviewer's comments: In an Advice letter dated October 22, 2004 and again at the EOP2 meeting, the Sponsor was instructed that the randomization and analyses be stratified and powered for subgroup analyses of ovarian reserve as measured by Day 3 serum FSH, age of the female partner and the type of insemination occurring (conventional in vitro fertilization versus intracytoplasmic injection). The Sponsor chose to ignore this advice.

On May 31, 2006, a preNDA meeting was held with the Sponsor. The Sponsor presented the initial results of the phase 3 clinical study (2004-02), and clarified that the non-inferiority limit for the Study 2004-02 was equal to or greater than -10% from the approved comparator (Crinone®).

2.6 Other Relevant Background Information

CLINICAL PHARMACOLOGY REGULATORY ACTIVITY:

On May 14, 2004, (in addition to the original proposal for a phase 3 protocol (2004-02), the Sponsor submitted a completed phase 1 protocol for Study 2004-01 entitled, "Title: "A Randomized, Open-Label, Pharmacokinetic, Pharmacodynamic and Tolerability Study of Three Dosage Strengths and Two Administration Regimens of a Vaginal Micronized Progesterone Tablet (Endometrin®) in Healthy Pre-Menopausal Female Subjects".

On July 1, 2004, Clinical Pharmacology and Clinical reviewers' comments on Study Protocol 2004-01 were sent in an Advice letter dated July 1, 2004. The Division's key clinical requests in the Advice letter for the phase 1 studies included:

1. Colposcopy should be performed on all subjects. All colposcopic findings should be recorded using standardized reporting instruments such as those listed in the 2000 World Health Organization (WHO) manual for standardized colposcopy.
2. If lesions or abrasions on the cervix or vagina are found at study termination or discontinuation, re-examination should be performed no later than 2-4 days. Subjects should be followed until their lesions resolve.
3. We recommend you record and categorize (i.e., dyspareunia, vaginal bleeding/spotting, etc.) subject reports of problems with intercourse during vaginal progesterone therapy.

In addition, the Clinical Pharmacology reviewer suggested excluding subjects who use vaginal creams in Study 2004-01. However, the Clinical Pharmacology reviewer added that a future pharmacokinetic (pK) study to examine the interaction of vaginal creams with the vaginal insert was recommended.

Reviewer's comment: The Sponsor proposed language in the label that would exclude the use of vaginal creams with Endometrin®. It is clinically likely that use of any vaginal cream would interfere with the dissolution of Endometrin®. Therefore, the clinical reviewer concludes that a study to determine the interaction between Endometrin® and vaginal creams is not necessary and that labeling is sufficient for this product.

At the February 28, 2005 EOP 2 meeting, the Sponsor proposed an additional pharmacokinetic study (Study 2005-08), and requested a determination from the Clinical Pharmacology Team whether there was concurrence that pharmacokinetic data from studies 2004-01, 2005-08 and sampling from the phase 3 study (2004-02) would be sufficient for NDA submission. The Clinical Pharmacology review team concurred with the Sponsor's proposal for collection of pharmacokinetic data for Endometrin® on May 16, 2006

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Micronized progesterone (progesterone, USP) is the active ingredient in Endometrin®. Each Endometrin® insert contains 100 mg of progesterone and contains the following inactive ingredients: colloidal silicone dioxide NF, lactose monohydrate NF, pregelatinized starch NF, polyvinylpyrrolidone USP, adipic acid FCC, sodium bicarbonate USP, sodium lauryl sulfate NF, magnesium stearate NF, _____ The drug substance progesterone is micronized and manufactured and supplied by _____ under

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DMF — Drug substance specifications, structure, container/closure system, and stability data are contained in DM —

Certificates of analysis for all of the drug substance and excipients have been provided by the respective supplier and drug substance manufacturer, _____

All of the excipients except for adipic acid conform to USP or NF requirements. Adipic acid is available as food grade (FCC) and is additionally tested against EP specifications and qualified for use in the formulation by the NDA holder.

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From a Chemistry, Manufacturing and Controls (CMC) standpoint, NDA 22-057/S-000 recommends approval pending the an acceptable cGMP on inspection from the Office of Compliance. Please see the Chemistry, Manufacturing and Controls Review for NDA 22-057/S-000 (Review date June 15, 2007).

A Product Quality Microbiology Review was conducted for NDA 22-057/S-000 to determine:

- o If the established microbial limits for Endometrin® were acceptable.
- o Whether Microbial Limits Testing should be included at stability
- o Whether the Limits for Water needed to be tightened
- o Whether the packaging line needed to be treated prior to manufacturing.

The Product Quality reviewer for Microbiology completed the review of Endometrin and determined that the application was approvable on condition that the Microbial Limits tests currently conducted at release must be performed at the Stability End Point (see review dated February 28, 2007).

Reviewer's comment: The CMC review team determined that the word tablet was not acceptable for a description of Endometrin® as it is administered vaginally. The CMC review team recommended that the word "insert" be used. This recommendation was used in this review and in the proposed label.

3.2 Animal Pharmacology/Toxicology

Progesterone is a steroid hormone that is a pharmacopeial substance with a previously documented pharmacological and toxicological profile. The excipients of effervescent progesterone are previously characterized pharmacopeial substances. The only nonclinical testing that was required for vaginally administered Endometrin® was topical and vaginal irritation studies to test the tolerability of the final drug product.

At the preIND meeting held on October 23, 2003, the Sponsor submitted several proposed nonclinical protocols for review. At that meeting, the Sponsor was informed, "To support the proposed clinical protocol for 14 days, a 14-day repeat dose vaginal irritation study should be conducted at multiple doses up to maximal feasible dose (MFD) in an appropriate species according to the ICH-M3 guidance. The study should be a complete toxicology study including histopathology of target organs, vagina and other reproductive organs, local draining lymph nodes (popliteal or inguinal) and include more than one dose.

All tissues should be collected and stored for future histopathological evaluation.” The Sponsor was encouraged at the meeting to submit the non-clinical study protocols for review and comment prior to conducting the study.

The Sponsor submitted a draft protocol for the 14-day rabbit study on December 10, 2003. The Pharmacology/Toxicology reviewer had a teleconference with the Sponsor on January 5, 2004 to discuss the submission and provide additional recommendations.

A teleconference was held on August 12, 2004 with for Pharmacology/Toxicology Guidance on a 90-day repeat dose toxicology draft study protocol entitled “90-Day Toxicity Study of Endometrin® Common Blend Administered by the Vaginal Route to Rabbits” (submission dated July 9, 2004). The Pharmacology Toxicology reviewer provided advice to the Sponsor on the volume and dose selection for Endometrin® for the 90-day rabbit study, a clarification of tissues that would be examined by histopathology in the 90-Day rabbit study, and discussed that pharmacokinetic data in terms of progesterone blood levels needed to be evaluated from a nonclinical study. The Pharmacology/Toxicology review team concluded at the meeting that the Sponsor could proceed with the 90-day study protocol and perform the progesterone determinations on blood samples stored from the 14-day toxicity study previously performed.

At the EOP2 meeting on February 28, 2005, the Sponsor submitted the initial results of the 90-day study. The Sponsor was informed that “We will need to independently review the histopathological findings that are observed in the 90-day study. After review of the 90-day study, if no safety issues are identified then we concur that no further nonclinical studies will be required to file a New Drug Application.”

The Pharmacology/Toxicology reviewer evaluated the nonclinical study reports submitted to IND 68,097 for Endometrin® in Amendment 018 (Letter date January 25, 2006) and Amendment 022 (Letter Day April 4, 2005) that included results of the 14-day vaginal irritation study in rabbits and the 90-day vaginal-irritation/toxicity study in rabbits. At that time, the Pharmacology/Toxicology reviewer concluded that “No further studies are necessary for the NDA submission”.

The NDA submission contained nonclinical toxicology studies that included: an acute dermal sensitization study in rabbits, a skin sensitization study in guinea pigs, and the final results of the 14- and 90-day vaginal irritation studies in rabbits.

The Pharmacology/Toxicology reviewer evaluated the final results of the four nonclinical toxicology studies and determined that these nonclinical studies showed minimal findings of toxicity. There were no significant findings of either dermal sensitization or vaginal irritation. The Pharmacology/Toxicology reviewer concluded that there were no unresolved toxicological issues and recommended approval. For more information, please see Pharmacology/ Toxicology Review for NDA 22-057/S-000 (see review dated May 14, 2007).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data used in this review is the single phase 3 clinical trial (2004-02) conducted by the Sponsor for the progesterone vaginal insert (Endometrin®). Study 2004-02 was an open-label (patient and investigator aware of study drug administered; only the ultrasonographer was blinded to treatment), active-controlled, clinical trial at 25 active sites was conducted in the US to support NDA 22-057. Study 2004-02 randomized at total of 1211 infertile subjects who were previously enrolled and screened, (mean age 33 years), to one of three parallel treatment groups. Subjects were treated for a total of 10-weeks of progesterone administered vaginally using either Endometrin® 100 mg inserts or Crinone® 8% gel.

Additional sources of clinical and pharmacokinetic data were obtained from two phase 1 pharmacokinetic studies conducted by the Sponsor (Ferring Pharmaceuticals) for the progesterone vaginal insert formulation. These studies evaluated the pharmacokinetic parameters of different doses (2004-01) and different regimens (2004-01 and 2005-08) of Endometrin®.

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Clinical Review
 {Audrey Gassman, MD}
 {NDA 22-057/S-000}
 {Progesterone vaginal insert}

4.2 Tables of Clinical Studies

Table 4: Table of Clinical Studies

Study Title	Endometrin®	Placebo	Safety Evaluations	Duration	To-Be-Marketed
Phase 3 Study: 2004-02 entitled, "A Multi-Center, Randomized, Open-Label, Parallel-Group Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) Compared to Crinone® 8% Vaginal Gel in Female Patients Undergoing In Vitro Fertilization (IVF)."	1211 total evaluable subjects (Endometrin® 100 mg BID - 404 subjects) (Endometrin® - 100 mg TID 404 subjects) (Crinone® 8%- 403 subjects)	Not applicable	Screening Visit (Visit 1) with a total of 6 additional visits (maximum) with adverse event review post-embryo transfer (Visit 3), 2 days post the 1 pregnancy test (Visit 3), 14 days post the 2 nd pregnancy test (Visit 5A) and at 6 weeks of gestation (Visit 5B) or end of study (Visit 6)	10 week treatment period	Yes
Phase 1 Studies: 2004-01 entitled: "A Randomized, Open-Label, Pharmacokinetic, Pharmacodynamic and Tolerability Study of Three Dosage Strengths and Two Administration Regimens of a Vaginal Micronized Progesterone Tablet (Endometrin®) in Health Pre-menopausal Female Subjects"	57 total evaluable subjects (Endometrin® 50 mg daily -9 subjects Endometrin® 100 mg daily - 11 subjects Endometrin® 200 mg daily-9 subjects Endometrin® 100mg twice daily - 9 subjects Endometrin® 200 mg twice daily- 10 subjects Progesterone in oil injection 50 mg daily - 10 subjects)	Not applicable	Screening visit (Visit 1) with a total of 10 additional visits (Up to Visit 11). PK sampling at Visits 6 through 10 at 36 hours post-dose, 48-hours post-dose, 72 hours post-dose, 96 hours post-dose, and 168 hours post-dose, respectively :	Maximum 10 day treatment period, study duration 38 days	Yes
2005-08 entitled: "A Randomized, Open-Label, Single and Multi-dose Pharmacokinetic Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) compared to Crinone® 8% Vaginal Gel in Healthy Pre-menopausal Female Subjects"	18 total evaluable subjects (Endometrin® 100 mg BID -6 subjects) (Endometrin® - 100 mg TID 6 subjects) (Crinone® 8%- 6 subjects)	Not applicable	Screening visit (Visit 1), followed by an overnight visit after 1 dose (Visit 2), then 5-dosing days (Visit 3) consisting of an overnight stay for approximately 6 nights (5 dosing days)	Maximum of 6 day treatment period, study duration 13 days including 7-day washout	Yes

4.3 Review Strategy

Sources used for preparing this review include the clinical studies listed above. Study 2004-02 is the primary efficacy study reviewed for the Sponsor's proposed indication of pregnancy through progesterone supplementation in women undergoing Assisted Reproductive Technology procedures. Study 2004-02 was determined to provide the primary efficacy and safety database for the proposed effervescent progesterone formulation. Additional safety information was also obtained from the two phase I pharmacokinetic studies (2004-01 and 2005-08) that used the effervescent progesterone formulation.

Two review issues were examined in detail:

1. Efficacy for the lowest progesterone dose (100 milligrams twice daily) tested in the primary phase 3 efficacy and safety Study 2004-02 for luteal support after Assisted Reproductive Technology therapy
2. Safety in terms of allergic reactions and vaginal irritation for both doses of Endometrin® (100 mg twice daily and 100 mg three times daily).

4.4 Data Quality and Integrity

Three sites were identified for a Division of Scientific Investigations (DSI) audit of the Sponsor's data and/or analyses. The following centers were proposed for audit based on the number of subjects enrolled, subjects discontinuations, and protocol violations:

- 1) Vicki Schnell, MD
Center for Reproductive Medicine
450 Medical Center Blvd Suite 202
Webster, TX 77598
Site 19
 - 2) Mostafa Abuzeid, MD
IVF Michigan
3950 S. Rochester Rd
Rochester Hills, MI 48307
Site 26
 - 3) Kevin Doody, MD
Center for Assisted Reproduction
1701 Park Place Ave
Bedford, TX 76022
Site 05
- For Site 05: The Good Clinical Practice Branch I (HFD-046) of DSI conducted a clinical inspection of site 5 (Dr. Kevin Doody) on October 30 – November 2, 2006. DSI concluded in a clinical inspection summary that “The inspection did not reveal any regulatory violations in the conduct of this study.” DSI concluded that the data appeared acceptable in support of the relevant indication. The final

classification for this site was No deviation from regulations – data acceptable (NAI).

- For Site 019: The Good Clinical Practice Branch I (HFD-046) of DSI conducted a clinical inspection of site 19 (Dr. Vicki Schnell) on November 14 -20, 2006. DSI concluded in a clinical inspection summary submitted on February 5, 2007 that “From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.” The final classification for this site was No deviation from regulations – data acceptable (NAI).
- For Site 026: The Good Clinical Practice Branch I (HFD-046) of DSI conducted a clinical inspection of site 26 (Dr. Mostafa Abuzeid) on October 16 – 26, 2006. DSI concluded in a clinical inspection summary submitted on February 9, 2007 with the following reported from DSI to the Division “Deviations from protocol were noted in that adverse events experienced by two subjects were not promptly reported to the IRB and sponsor..... The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.” The final classification for this site was VAI – No Response Requested – Data acceptable.

The overall DSI assessment of findings and general recommendations (dated February 20, 2007) stated that “The inspections of Drs. Doody and Schnell did not identify any regulatory violations. The inspection of Dr. Abuzeid noted two subjects who experienced adverse events that were not promptly reported. Overall, the data appear acceptable in support of the respective indication.”

4.5 Compliance with Good Clinical Practices

Study 2004-02, the phase 3 study, appears to have been conducted in accordance with regulations pertaining to Good Clinical Practice (GCP) (International Conference on Harmonization: Good Clinical Practice Consolidation Guidelines, Notice of Availability, *Federal Register* 25692, May 6, 1997) and the Declaration of Helsinki (revised Hong Kong, 1989).

An informed consent form was signed and dated by the subject, a witness, and the investigator during screening as specified in the study protocol. The original signed informed consent form was retained in the subject’s study file by the Investigator.

Reviewer’s comment: A sample informed consent form for Study 2004-02 was included in the NDA submission (pages 810 – 820 of 7469) and appeared adequate.

A total of 1504 subjects were screened for the study at 25 clinical sites. A total of 155 of the 1504 subjects were screening failures (10.3%). Of the 1349 subjects that began down-regulation with a gonadotropin-releasing hormone agonist, 138 of 1349 (10%) were discontinued from the study for the following reasons: 27 were down-regulation failures,

63 were stimulation failures and 48 subjects were “dropped” prior to randomization. Therefore, 1211 (80.5% of the original screened 1504) subjects successfully completed down-regulation and ovarian stimulation, and were randomized in Study 2004-02.

Reviewer’s comment: In Study 2004-02, 138 subjects of the 1349 that initiated ART treatment were discontinued prior to oocyte retrieval (10%). This 10% discontinuation rate post-screening is acceptable, based on the published 2002 Assisted Reproductive Technology Success Rates that report that approximately 12% of ART cycles were discontinued prior to egg retrieval.¹

Of the 1211 randomized subjects (who completed ovarian stimulation), 465 became pregnant and completed the 10 total treatment weeks (38.4%) with either Endometrin® or Crinone®. No clinically significant differences were seen between the two Endometrin® treatment groups and the Crinone® group in proportion of subjects who failed to complete the study (245 of 404 [61%] in the Endometrin® twice daily group, 232 of 404 [57%] in the Endometrin® three times daily group and 233 of 403 [58%] in the Crinone® group). The most common reason for discontinuation was lack of a positive pregnancy test at Visit 3 or 4 across the three treatment groups (201 of 404 [50%] in the Endometrin® twice daily group, 163 of 404 [40%] in the Endometrin® three times daily group and 184 of 403 [46%] in the Crinone® group).

4.6 Financial Disclosures

Form FDA 3454 (703), dated August 21, 2006, signed by James H. Conover, Ph.D. Executive Director, Regulatory Affairs for Ferring Pharmaceuticals, Inc. was included in the submission. None of the 29 listed investigators and 60 listed sub-investigators was the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetic studies performed by the Sponsor included:

Study 2004-01: entitled, “A Randomized, Open-Label, Pharmacokinetic, Pharmacodynamic and Tolerability Study of Three Dosage Strengths and Two Administration Regimens of a Vaginal Micronized Progesterone Tablet (Endometrin®) in Healthy Pre-menopausal Female Subjects”

¹National Center for Chronic Disease Prevention and Health Promotion of the Center for Disease Control. 2002 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. December 2006

This phase 1, open-label, clinical trial was conducted at two study sites

┆ The objectives of 2004-01 included:

- Evaluating the pharmacokinetic parameters of Endometrin® after single and multiple dose pharmacokinetic parameters.
- Evaluate the dose-response relationship on endometrial development
- Determine the onset of steady-state with the multiple dose-regimens
- Obtain tolerability information on the product

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The six treatment groups are outlined in Table 5 and included:

Table 5: Treatment Groups for Study 2004-01

Treatment group	Dose	Administration (same time daily)
Endometrin® (n= 9)	50 mg once daily	One insert vaginally each morning
Endometrin® (n=11)	100 mg once daily	One insert vaginally each morning
Endometrin® (n=9)	200 mg once daily	Two inserts vaginally each morning
Endometrin® (n=9)	100 mg twice daily	One insert vaginally each morning and one insert vaginally each evening
Endometrin® (n=10)	200 mg twice daily	Two inserts vaginally each morning and one insert each evening
Injectable progesterone (n=10)	50 mg/mL – 1mL injected once daily	One injection into the buttock once daily

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-01, Table 3, page 37 of 1625.

This study enrolled 58 healthy premenopausal women with regular menstrual cycles (between 18 and 40 years of age who had menstrual cycles between 24 to 35 days). Each subject in Study 2004-01 was required to complete a total of 11 visits that included 2 overnight visits for blood sampling and endometrial assessment. The approximately duration of study participation was 38 days, with 10 days of treatment with a progesterone product.

Subjects in Study 2004-01 were evaluated during four phases: Screening, Down-Regulation, Estrogen Priming and Randomization/Treatment.

- Screening phase: Screening procedures (Visit 1) included obtaining informed consent, medical history, physical examination (including gynecological examination), safety laboratories and colposcopy.
- Down-regulation phase: Subjects who met the inclusion/exclusion criteria for screening and had completed screening procedures (Visit 2) received a single intramuscular injection of 3.75 mg of Lupron® Depot (leuprolide acetate) in the luteal phase to suppress endogenous hormonal production. The subject returned on the 3rd to 5th day of menstrual bleeding after her Lupron® injection for a visit (Visit 3). For eligibility to being the Estrogen priming, the subject's serum

estradiol was to be ≤ 50 pg/mL and her endometrial lining was to be ≤ 7 mm at Visit 3.

- Estrogen priming phase: Subjects who successfully met the criteria for down-regulation then received 14 days of estradiol transdermal patches (Climara® 0.1 mg) for a total of 14 days (1 patch for 4 days, 2 patches for 5 days and 3 patches for 5 days). Subjects returned to the study center on Day 14 of estradiol therapy for blood work and a repeat ultrasound. Subjects could proceed into the Randomization/treatment phase with progesterone if the subject met the following criteria: 1) Serum progesterone ≤ 1 ng/mL and 2) a transvaginal ultrasound demonstrating an endometrial lining measurement of ≥ 7 mm.
- Randomization/Treatment phase: Subjects who completed the estrogen priming phase were then randomized to one of the 6 treatment groups to receive 10 days of progesterone therapy. Subjects in the Endometrin® daily dose groups were to insert Endometrin® vaginally at the same time each morning for 10 days, subjects in the twice daily group were to insert Endometrin® each morning and evening for 10 days vaginally. Subjects in the injectable progesterone group were to inject themselves in the buttock with 50 mg of progesterone once each morning for 10 days. All subjects continued to apply one Climara® patch per week for the 10 day treatment period.

Pharmacokinetic analysis of the 10-day progesterone treatment was performed at the time of the first day and tenth day doses. Blood samples for pharmacokinetic analysis were obtained:

- Day 1: Prior to the first progesterone dose and then at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 168 hours post-dose.
- Day 10: Prior to the last progesterone dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose.

Endometrial biopsies were performed at the Final Visit on Treatment Day 10 \pm (Cycle Day 24/25).

The mean serum progesterone pharmacokinetic parameters of Endometrin® in each treatment group at Day 10 as calculated by the Sponsor included:

<u>Progesterone</u> <u>(pg.hr/ml)</u>	<u>C_{max} (pg/ml)</u>	<u>T_{max} (h)</u>	<u>AUC_{0-T}</u>
50 mg Endometrin® daily	6.59	5.44	45.7
100 mg Endometrin® daily	7.70	5.45	58.8
200 mg Endometrin® daily	13.2	3.31	89.7
100 mg Endometrin® twice daily	12.5	4.73	102
200 mg Endometrin® twice daily	13.0	5.88	99.6
Progesterone injection (50 mg/mL)	30.3	7.15	485

The Sponsor concluded that pharmacokinetic assessment in Study 2004-01 demonstrated that:

- Steady state was reached with 24 hours using Endometrin®.

- Concentrations reached peak levels approximately 8 to 12 hours after insert administration.
- Mean trough concentrations indicated that steady state was achieved before the end of 10 days of therapy.
- Peak concentrations did not show a well-defined dose-proportionality following the first dose of progesterone. The mean C_{max} for the 200 mg once daily group and the 200 mg twice daily group were only approximately 40% greater than the C_{max} of the respective 100 mg groups, not by two-fold as expected on the basis of dose-proportionality.

Study 2005-08: entitled “A Randomized, Open-Label, Single and Multidose (Single Day and Multiple Day) Pharmacokinetic Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) compared to Crinone® 8% Vaginal Gel in Healthy Pre-menopausal Female Subjects”.

This phase I, open-label, clinical trial was conducted at only one study site _____
 The primary objective of Study 2005-08 was to evaluate the pharmacokinetic parameters of 100 mg Endometrin® inserts after two different dosing regimens (100 mg twice daily and 100 mg three times daily).

b(4)

The three treatment groups are outlined in Table 6 and included:

Table 6: Treatment groups for Study 2005-08:

Treatment group	Dose	Administration (same time daily)
Endometrin® (n= 6)	100 mg twice daily	One insert administered vaginally 12 hours apart
Endometrin® (n=6)	100 mg three times daily	One insert administered vaginally 8 hours apart
Crinone 8% gel (n=6)	90 mg once daily	One gel applicator inserted vaginally each day

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2005-08, Table 4, page 30 of 857.

This study enrolled 18 healthy premenopausal women with regular menstrual cycles (between 18 and 40 years of age who had menstrual cycles between 24 to 35 days). Each subject was required to complete 3 total visits that included 2 overnight visits for blood sampling. Subjects were treatment in four phases: Screening, Single-day, Washout, and Multiple dose.

- Screening: Screening procedures (Visit 1) included obtaining informed consent, medical history, physical history (including gynecological examination), and safety laboratories.
- Single Dose: Subjects were randomly assigned to one of the three treatment groups between Cycle Days 5 and 8 of their menstrual cycle. Subjects then received assigned study drug for 1 day (single dose for the once daily treatment,

two doses 12 hours for the twice daily treatment, and 3 doses 8 hours apart for the three times daily treatment).

- Washout: the subject was then discharged and completed a 7 day without progesterone.
- Multiple-Dose: All subjects then returned to the clinical for approximately 6 overnight stays. Subjects were treated for five consecutive days with progesterone (Endometrin® twice daily, Endometrin® three times daily or Crinone® once daily).

Pharmacokinetic analysis of the 6 total days of progesterone treatment was performed at the time of the first day dosing and again during a separate 5-day dosing period. Blood samples for pharmacokinetic analysis were obtained:

- Single day dosing: Prior to dosing (0), 2, 4, 8, 12, 16, 24, 36 and 48 hours following the first dose of medication.
- Multiple day dosing: Prior to dosing, then on days 1 through 4 - at 6 and 12 hours for subjects in the Endometrin® twice daily group, at 6 and 8 hours for the subjects in the Endometrin® three times daily group. Subjects in the Crinone® group had blood samples at 6, 12, and 24 hours on Days 1 through 3 and at 6 and 12 hours on Day 4. On Day 5 of treatment, blood samples were obtained in all subjects at 0, 2, 4, 8, 12, 16, 36 and 48 hours after first dosing.

The Sponsor concluded that Study 2005-08 demonstrated that:

- Progesterone serum concentrations reached steady-state values approximately 1 day after initiation of treatment with Endometrin®.
- The Endometrin® twice daily treatment provided a systemic exposure on Day 5 of AUC_{0-24} was 327 ng*hr/mL in the Endometrin® twice daily group and 436 ng*hr/mL in the Endometrin® three times daily group as compared to 264 ng*hr/mL in the Crinone® group.
- The three treatment progesterone regimens produced relatively uniform 24-hour concentration-time profiles, with the lowest concentrations of the day (C_{min}) averaging 40-50% of the peak concentration (C_{max}) for all three regimens.
- The two Endometrin® regimens exceeded serum progesterone levels of 10 ng/mL (a serum progesterone level reported to be consistent with acceptable ovulation) during Day 5 sampling. The mean progesterone concentrations for Endometrin® twice daily administration on Day 5 were 11-17 ng/mL and for Endometrin® three times daily administration were 14-24 ng/mL.

Reviewer's comment: The pharmacokinetic and pharmacodynamic results for Studies 2004-01 and 2005-08 were reviewed by the Clinical Pharmacology reviewer and found to be acceptable. The Clinical Reviewer recommended approval of the application for Endometrin® on May 24, 2007. For more information on Studies 2004-01 and 2005-08, see the Clinical Pharmacology Review of NDA 22-057.

A pharmacokinetic sub-study of the phase 3 Study 2004-02 was performed during the 10-week primary phase 3 study (2004-02). Study FPI-2004-02, entitled, "Comparative

Pharmacokinetics of Progesterone Administered as Endometrin® BID, Endometrin® TID or Crinone® QD in Female IVF Patients”.

This open-label sub-study was conducted at two clinical sites (Site #21 - _____ and Site #26 _____). The primary objective of this sub-study was to compare the serum pharmacokinetics of progesterone following the exogenous administration of each of the three treatment regimens in Study 2004-02 in pre-menopausal females undergoing Assisted Reproductive Technology procedures. **b(4)**

The sub-study enrolled 27 subjects that had met the inclusion/exclusion/screening criteria for Study 2004-02. The unequal number of subjects enrolled in the sub-study was a result of the treatment randomization that was performed for all study sites and included:

- Endometrin® 100 mg three times daily (N=7)
- Endometrin® 100 mg three times daily (N=8)
- Crinone® 8% vaginal gel once daily (N=12)

Serum progesterone pharmacokinetics was assessed throughout treatment in these 27 subjects, with frequent sampling and infrequent sampling for as long as 10 total weeks (maximum treatment duration for progesterone therapy). Sampling visits for the pharmacokinetic sub-study of Study 2004-02 are outlined in Table 7 and included:

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Table 7: Schedule of Assessments for Pharmacokinetic Assessments during Study 2004-02

Time Point	Estradiol and Progesterone	Transvaginal Ultrasound*
Day of hCG administration	1 sample	Yes
Day following hCG administration (every 4 hours for 12 hours)	4 samples	Yes
Day of oocyte retrieval (every 4 hours for 12 hours)	4 samples	Yes
Day 3 post-retrieval (4 hours post morning progesterone dose)	1 sample	Yes
Day 5 post-retrieval (every hour for 12 hours)	13 samples	Yes
Day 7 post-retrieval (4 hours post-morning progesterone dose)	1 sample	Yes
Weekly thereafter until treatment is completed (Day 14, 21, 28, 35, 42, 49, 56, 63, 70) – all 4 hours post morning progesterone dose	1 sample each timepoint	Yes

*Study 2004-02 procedures unrelated to pharmacokinetic assessment for subjects in the sub-study.
 Source: Adapted from NDA 22-057/S-000, Final Report for Comparative Pharmacokinetic assessments during Study 2004-02, Schedule of Assessments, page 2085 of 7469.

Maximum progesterone concentrations (C_{max}) and minimum concentrations (C_{min}) were determined on Day 7 (fifth day of treatment), the day with 12-hours of comprehensive sampling, without interpolation. Based on the results of the progesterone sampling, the Sponsor concluded:

- Mean serum progesterone concentrations increased by 50 ng/mL between Day 2 and Days 5 through 7. Administration of exogenous progesterone and increased endogenous progesterone production secondary to ovarian stimulation contributed to the increased progesterone levels.
- The three treatment regimes produced relatively uniform 12-hour concentration-time profiles on Day 7, with the lowest concentration averaging between 56-76% of the peak concentration for all three treatment regimes.
- Patients that became pregnant had elevated serum progesterone levels for at least 10 weeks, with no treatment-related differences in the observed levels for the three different treatment regimens. Serum progesterone levels were somewhat lower during Week 10 than on Days 5-7, around the time of implantation.
- Before discontinuing treatment, progesterone levels dropped significantly in subjects that did not become pregnant. Progesterone levels in subjects on medication but not pregnant on Day 16 were similar to levels in a previous study of healthy pre-menopausal women receiving the same three treatments for 5 days (2005-08).

- All three treatment arms obtained mean progesterone levels over 10 ng/mL. This progesterone threshold is associated with adequate ovulation under physiologic conditions. However, statistical differences between the three progesterone treatment arms were not statistically significantly different at any of the sampling time points.

Reviewer's comment: The reviewer agrees with the Sponsor that identification of statistically significant treatment-related differences in serum progesterone in this pharmacokinetic study 2004-02 is not possible based on: 1) the small number of subjects in the pharmacokinetic sub-study, and 2) the intrinsic intra-patient variability in endogenous progesterone production that potentially masked treatment effects and 3) the initial endogenous boost of progesterone from the hCG injection post-retrieval. Therefore, although serum levels of Endometrin® three times daily were somewhat higher than Crinone®, no claims of pharmacokinetic or pharmacodynamic advantage for Endometrin® can be made based on this limited population pharmacokinetic information.

5.2 Pharmacodynamics

Pharmacodynamic assessments were performed in Study 2004-01 as adjuncts to the pharmacokinetic evaluation of serum progesterone. The pharmacodynamic parameters evaluated included: secretory transformation by endometrial biopsy, tissue levels of progesterone, intensity and percent of progesterone and estrogen receptor content, and endometrial thickness measurements on ultrasound.

The key pharmacodynamic parameter evaluated in addition to serum progesterone levels was secretory transformation as determined by endometrial biopsy, and was considered by the Sponsor to be the basis for the pharmacodynamic assessment. Endometrial biopsies were performed on healthy pre-menopausal subjects who had been previously down-regulated, were primed with estrogen. Estrogen priming was determined by a transvaginal ultrasound endometrial measurement of ≥ 7 mm or a determination by the Medical Monitor that a complete evaluation of the endometrial lining and serum estradiol measurement(s) was adequate.

After down-regulation and determination of adequate estrogen priming, subjects were randomized to one of 6 different progesterone dose groups. Each subject was treated with approximately 10-days of progesterone study medication prior to endometrial biopsy. Each dose and regimen of Endometrin® was assessed for secretory transformation of the endometrium on Cycle day 24 or 25 of the Treatment Phase (Treatment Day 10 ± 1). The endometrial histology reported is outlined in Table 8:

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Table 8: Summary of Endometrial Biopsy Results from Study 2004-01

Category	Endometrin® 50 mg QD* (N=9)	Endometrin® 100 mg QD* (N=11)	Endometrin ® 200 mg QD* (N=9)	Endometrin ® 100 mg BID* (N=8)	Endometrin® 200 mg BID** (N=10)	IM P† 50 mg/mL QD* (N=10)
Secretory	1	1	4	5	6	9
Proliferative	2	3	2	1	1	0
Nonsecretory/ "Breakdown bleeding"	6	5	3	1	2	1
Inactive	0	2	0	1	1	0

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-01, Table 14.3.4.5, page 150 of 1625.

†Injectable progesterone in oil

*QD - Once daily

** BID - Twice daily

The Sponsor noted that the majority of subjects in Study 2004-01 who were treated in the twice daily Endometrin® treatment groups had a secretory phase biopsy result, while no consistent pattern was seen in the Endometrin® 200 mg once daily group.

Reviewer's comments:

1. *The reviewer agrees with the Sponsor that from the histologic results of Study 2004-01 that:*

- *Once daily dosing produces changes more consistent with proliferative endometrium rather than the desired secretory histology.*
- *Twice daily dosing demonstrated secretory changes in a majority of the subjects*
- *No disordered proliferative, hyperplastic or other significantly abnormal histologic pathology was reported*

Based on this limited data, the reviewer agrees with the Sponsor that twice daily dosing appears to produce the desired secretory changes. This reviewer believes that if the Sponsor had required all subjects to have had an endometrial lining of > 7 mm and a serum estradiol level of > 50 pg/mL, more consistent endometrial histology results would have been found across the treatment groups.

2. *The Sponsor raised concerns that endometrial histology may not be a valid clinical tool or a critical endpoint for implantation. The reviewer agrees that there are still questions whether endometrial dating is useful or correlates with pregnancy outcomes. However, determination of secretory endometrium as a pharmacodynamic endpoint for progesterone has historical precedence as a surrogate endpoint previously. Although assays for progesterone receptors and tissue progesterone levels are available, the reviewer does not feel that the results of these assays have been standardized or are adequately correlated with*

pregnancy outcomes. Therefore, these assays are still experimental with respect to modeling for progesterone dose-finding.

No pharmacodynamic assessments were performed in Study 2005-08.

5.3 Exposure-Response Relationships

Each Endometrin® insert contains 100 mg of micronized progesterone. Prior to the conduct of the two phase 1 Studies 2004-01 and 2005-08, no dose-finding data for Endometrin® was available. Additional pharmacokinetic data was provided by a small sub-study of Study 2004-02 in 27 previously enrolled subjects in the three treatment arms.

Reviewer's comment: The phase 3 data was unusable to determine an exposure-response relationship as endogenous progesterone from the ovary may have masked actual exposure from Endometrin®. Therefore, exposure information is obtained from the two phase 1 studies (2004-01 and 2005-08). Based on this information, the selection of Endometrium 100 mg twice daily and three times daily appear to have been acceptable for the overall patient population for the primary phase 3 Study 2004-02. Of note, the Phase 1 studies did not determine potential dosing for any of the sub-groups (such as those subjects with an FSH between 10 and 15 IU/L or subjects who were age 35 and older) that were treated in this Study 2004-02.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor submitted NDA 22-057/S-000 electronically, on August 21, 2006. The Sponsor requested approval of both daily dosage regimens (100 mg twice daily and 100 mg three times daily) of Endometrin® Vaginal Inserts for pregnancy through progesterone supplementation as part of an Assisted Reproductive Technology program for infertile women.

Reviewer's comment: The following revised indication was proposed to the Sponsor, "Endometrin® is a progesterone indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women" to better define the indication.

6.1.1 Methods

Study 2004-02 was the single, phase 3 study conducted to evaluate the safety and effectiveness of Endometrin®. In addition to primary phase 3 Study 2004-02, two phase 1 Studies (2004-01 and 2005-08) were conducted to assess the single-dose and multiple-

dose pharmacokinetics of progesterone inserts given in different doses and regimens in healthy pre-menopausal women.

No efficacy data was generated in studies 2004-01 or 2005-08 as these were performed in a different patient population for short durations. Adverse events reported in studies 2004-01 and 2005-08 were reviewed for the clinical summary of safety.

Reviewer's comment: The two phase 1 pharmacokinetic studies (2004-01 and 2005-08) exposed subjects to very short durations of Endometrin® use and were in a different patient population and therefore inadequate to provide additional efficacy data.

6.1.2 General Discussion of Endpoints

The Center for Disease Control (CDC) publishes the current standard reporting terminology for reporting success rates for Assisted Reproductive Technology therapies in the United States.² In the most current (2002) edition, "success rates" were reported by the following methodologies:

- Pregnancy per cycle
- Live birth per cycle rate
- Live birth per egg retrieval rate
- Live birth per transfer rate
- Singleton livebirth per cycle rate
- Singleton livebirth per transfer rate

The Division believes that success rates for labeling of luteal supplementation should be consistent with recommendations of success for ART from the CDC. Therefore, the Division has previously recommended use of "clinical pregnancy rate" (defined as a pregnancy documented by ultrasound with a fetal heartbeat") as the primary endpoint for proposed studies for gonadotropins for ovarian stimulation and luteal supplementation.

Reviewer's comments:

1. *The Sponsor chose to use the primary efficacy endpoint of "ongoing pregnancy" defined as identification of fetal heart movement at approximately 6 weeks of gestation (6 weeks post-transfer) following an Assisted Reproductive Technology treatment cycle. The reviewer agrees that the primary efficacy endpoint is acceptable for the general indication of luteal supplementation.*
2. *The Sponsor's randomization was after oocyte retrieval. Therefore it is important to note that the ongoing pregnancy rates reported are per retrieval, not per cycle. Pregnancies per retrieval are slightly higher than per cycle as the denominator is lower per retrieval. Pregnancy outcomes in this review are listed as per retrieval to prevent inaccurate comparisons to pregnancy outcome data in other studies and reports that may use a different denominator. In fact, the CDC Assisted*

²Center for Disease Control and Prevention. 2002 Assisted Technology Success Rates. Palladian Partners Inc. December 2004.

Reproductive Technology Success rates for the United States are listed per cycle, not per retrieval. Therefore, it is expected that the Sponsor would see slightly higher rates than other publications including the CDC have reported for ongoing pregnancy and live births.

6.1.3 Study Design

Phase 3 Study 2004-02 was a 12-week, open-label (only the ultrasonographer was blinded therefore the study was not a true assessor-blind), active-controlled clinical trial in which a total of 1211 healthy women who had completed down-regulation, ovarian stimulation and oocyte retrieval, were randomized to one of three treatment groups:

- Endometrin® 100 mg inserts administered twice daily (A total of 200 mg of progesterone per day) vaginally for 10 weeks from the day after oocyte retrieval; N = 404.
- Endometrin® 100 mg inserts administered three times daily (A total of 300 mg of progesterone per day) vaginally for 10 weeks from the day after oocyte retrieval; N = 404.
- Crinone® 8% intravaginal gel applied once daily (90 mg of progesterone per day) for 10 weeks from the day after oocyte retrieval N = 403.

The primary objective of the final protocol for Study 2004-02 (Protocol Amendment 2) was to compare the efficacy of two different dosing regimens of Endometrin® (100 mg twice daily and 100 mg three times daily) compared to a matching progesterone gel (Crinone 8%) using the ongoing pregnancy rate (pregnancy identified on ultrasound with at least one gestational sac with a fetal heart beat present at approximately 6 weeks of gestation). Enrollment for Study 2004-02 began on July 18, 2005.

Other secondary objectives for Study 2004-02 included rates of: biochemical pregnancy (positive serum β -human chorionic gonadotropin levels at 12-14 days post-embryo transfer), clinical pregnancy [presence of gestational sac at 4 weeks gestation (4 weeks post-transfer)], live births, spontaneous abortions, ectopic pregnancies, cycle cancellations and genital bleeding.

There were two Amendments for Study 2004-02. Amendment 1 was dated June 17, 2005, approximately one month before the study began. This Amendment contained the key following protocol changes:

- Deleted requirements for obtaining pretreatment testosterone, dehydroepiandrosterone sulfate (DHEAS) and varicella as this was not standard practice at investigational sites.
- Allowed intracytoplasmic injection and assisted hatching.
- Extended the window for randomization of a subject to the day of oocyte retrieval or the day following oocyte retrieval at the request of the investigators

- Added a five day window for follow-up visits (3 [post-embryo transfer visit] and 5A [ultrasound after 2nd positive pregnancy test] at the request of the investigators
- Allowed smokers to participate
- Excluded subjects that used any of the following medications during the pretreatment or treatment phase: hormonal products except for oral contraceptives for down-regulation, progesterone creams, hydrocortisone, and fertility modifiers including insulin sensitizers
- History of recurrent pregnancy loss defined as 3 or more spontaneous miscarriages

Amendment 2 was dated January 13, 2006, approximately 6 months after subjects began enrolling in Study 2004-02. The three study changes noted between Protocol Amendment 1 and 2 included:

- Clarified that there would be no fewer than 330 subjects randomized per treatment arm.
- Allowing an individual site to enroll up to 150 subjects (previous cap was 100 subjects).
- Defined the per protocol population as subjects without major protocol violations who did not receive any other medication for luteal support other than the injection of human chorionic gonadotropin for oocyte maturation.

Reviewer's comment: Although the increases in overall subject population and subject enrollment per site occurred after the start of Study 2004-02, the reviewer does not believe that these changes significantly impacted the study results or outcome.

The study design for the final protocol as outlined in Amendment 2 for Study 2004-02 was acceptable based on the Sponsor's general compliance with the majority of recommendations from the Division during development. Study 2004-02 was open-label, assessor-blind, active-controlled, and of a 10-week treatment duration. Overall, the phase 3 Study 2004-02 as outlined in Protocol Amendment 2 was adequate and controlled, incorporated appropriate inclusion and exclusion criteria, and was of adequate duration for the general indication of luteal support after Assisted Reproductive Technology procedures.

Reviewer's comments:

1. *The Division initially recommended that the Sponsor perform a double-blind, double-dummy study using an approved progesterone product for a comparator (Crinone®) in an Advice letter on October 22, 2004 for the primary phase 3 Study 2004-02. The Sponsor then raised concerns that the insert and gel formulations of the two vaginal products were very different and a double-dummy study would interfere with each product's absorption and pharmacokinetic characteristics.*
2. *At the EOP2 meeting on February 28, 2005 the Division agreed that Study 2004-02 should therefore be conducted as an assessor blind study and*

more specifically, that no individual who is making any decisions (investigator or ultrasonographer) should be aware of treatment. The Sponsor did not follow the Division's recommendation at the EOP2 meeting and the study blinded only the person performing the transvaginal ultrasounds to confirm clinical and ongoing pregnancies, while the patient and investigator were not blinded. The reviewer had concerns as the subjects and investigators knew what treatment they were on bias in terms of monitoring could have occurred. Had the randomization occurred at cycle start, this reviewer would not have accepted this study as there would have been too high a possibility of bias in the study. However, as this study randomized subjects after retrieval, and with a low discontinuation rate this was acceptable although not optimal. This reviewer still feels strongly that the study should have been both investigator and ultrasonographer blinded to minimize any potential bias in monitoring or reporting adverse events.

6.1.4 Efficacy Findings

Study 2004-02, the primary phase 3 study, was a randomized, open-label (only the ultrasonographer was blinded), active-controlled, 10-week clinical trial conducted to compare two dosing regimens of 100 mg of Endometrin® (twice daily and three times daily) to Crinone® 8% gel in subjects undergoing Assisted Reproductive Technology (ART) therapy. A total of 1211 subjects were randomized (404 to the Endometrin® twice daily treatment group, 404 to the Endometrin® three times daily group and 403 to the Crinone® treatment group). There were a maximum of 8 scheduled clinic visits during the clinical study: two screening visits (Visit 1 and a post-screening visit) and up to 6 treatment visits (Visits 2, 3, 4, and 5A, 5B and 6 on day of oocyte retrieval, 14 days [\pm 5] post-embryo transfer, 2 days after the 1st positive serum pregnancy test, 14 days after the 1st positive pregnancy test, at 6 weeks of gestation [if needed] or day of last dose [final visit], respectively).

Randomization for Study 2004-02 took place using a phone based electronic Interactive Voice Response System (IVRS). On the day of subject randomization (day of oocyte retrieval or the day following), the IVRS would randomly assign each subject to one of three treatment groups after phone contact from the site. The randomization code was generated using SAS software. The IVRS was programmed to ensure an equal number of subjects per treatment group and stratification for age and serum FSH level.

Reviewer's comments:

- 1. No major changes made to the number of clinic visits or randomization scheme from study initiation (under Protocol Amendment 1) to initiation of Protocol Amendment 2 final protocol).*
- 2. The study would have been optimally designed if randomization had also been stratified for type of assisted reproductive technology therapy (i.e. in vitro fertilization [IVF] compared to intracytoplasmic injection [ISCI]). These two*

different procedures may have different baseline pregnancy rates in some patient populations (subjects with male factor infertility over 40 and all subjects with non-male factor infertility who used ICSI compared to IVF). However, the reviewer noted that the number of subjects who had IVF or ICSI was roughly similar across the treatment groups.

- 3. The reviewer also has concerns that allowing assisted hatching and allowing Day 3 or Day 5 embryo transfer could have impacted ongoing pregnancy rates. No stratification was performed for these variables.*
- 4. The Division had previously asked the sponsor to perform a stratification at randomization for type of insemination procedure. The Division advised that the analyses did not need to be powered to demonstrate a difference unless specific claims were requested.*

6.1.4.1 Inclusion and Exclusion Criteria

Study 2004-02 included healthy pre-menopausal women age 18 to 42 with a history of infertility and requiring assisted reproductive technology therapy. Key inclusion criteria included an early follicular phase serum follicle stimulating hormone (FSH) level of ≤ 15 IU/L, a documented history of infertility (unable to conceive for at least one year or for 6 months for women ≥ 38 years of age or bilateral tubal occlusion or absence), male partner with recent (within 6 months prior to screening) semen analysis by standard WHO and/or Kruger criteria, at least one cycle with no fertility medication prior to screening a hysterosalpingogram, hysteroscopy or sonohysterogram documenting a normal uterine cavity, and a negative pregnancy test on the day of pituitary down-regulation prior to administration of gonadotropin-releasing hormone agonist.

Potential study participants were excluded for the following key reasons: donor oocyte or embryo recipient, undergoing blastomere biopsy or other experimental procedure, inadequate number of oocytes (defined as fewer than 3 oocytes retrieved in the study cycle), presence of any clinically relevant systemic disease (e.g. insulin-dependent diabetes mellitus), subjects with a body mass index $> 34 \text{ kg/m}^2$ at screening, previous in vitro fertilization or assisted reproductive technology failure due to a poor response to gonadotropins (defined as development of ≤ 2 mature follicles or history of 2 previous cycle cancellations to oocyte retrieval due to poor response), presence of abnormal uterine bleeding of unknown origin, for male partner – obvious leukospermia (> 2 million WBC/mL) or signs of infection in semen sample within past 2 months of pituitary down-regulation, use of any of the following medications during pretreatment and treatment: hormonal products (use of oral contraceptives during down-regulation allowed), progesterone creams, hydrocortisone and other steroid products, and fertility modifiers including insulin sensitizing agents, and history of recurrent pregnancy loss defined as three or more spontaneous miscarriages.

Reviewer's comment: The inclusion and exclusion criteria were generally appropriate for a clinical trial for luteal supplementation. However, the Division's original Advice letter (dated October 22, 2004) requested that the Sponsor exclude subjects with a body mass

index > 38 kg/m² as opposed to > 34 kg/m² to more closely reflect the current patient population in the United States. At this point, dosing of Endometrin® for obese subjects is unknown. Therefore, the weight restrictions seen in Study 2004-02 should be noted in the CLINICAL STUDIES section of labeling.

Potential study participants were withdrawn if they met the following criteria: treatment failure (defined as not reaching a standard follicular and hormonal criteria for oocytes retrieval), inadequate number of oocytes retrieved (less than 3 oocytes retrieved), cycle cancelled for risk of ovarian hyperstimulation syndrome, and had major protocol violations (including noncompliance) or used other drug products for luteal supplementation.

Reviewer's comment: The changes to the inclusion/exclusion/withdrawal criteria that occurred with the initiation of the revised protocol in Amendment 2 are unlikely to have significantly changed the recruited study population as compared to those recruited under Amendment 1. Therefore, subjects recruited under Protocol Amendment 1 will be analyzed concomitantly with subjects recruited under the final protocol as outlined in Protocol Amendment 2.

6.1.4.2 Study Medication

Clinical Trial Services (Audubon, PA) supplied clinical supplies. Study products included:

- Endometrin® 100 mg inserts applied vaginally twice daily
- Endometrin® 100 mg inserts applied vaginally three times daily
- Crinone® 8% gel (reference therapy) applied vaginally once daily

The Sponsor provided the gonadotropins for stimulation, although the gonadotropins were administered in accordance with the Assisted Reproductive Technology protocol guidelines at each individual site. All subjects also received a single injection of human chorionic gonadotropin (Novarel® 5,000 – 10,000 USP units) intramuscularly to trigger ovulation. A total of three active treatment regimens containing progesterone for luteal supplementation were utilized in Study 2004-02.

6.1.4.3 Subject Disposition

For Study 2004-02, the Intent-to-Treat (ITT) population included all subjects who were randomized to treatment who met the following criteria: met the inclusion/exclusion criteria, undergone successful screening procedures, completed both down-regulation, and ovarian stimulation successfully, and took at least one dose of study drug. Table 9 provides a summary of the disposition of the study subjects and the subject cohorts:

Table 9: Summary of subject disposition in Study 2004-02

	Endometrin® 100 mg twice daily	Endometrin® 100 mg three times daily	Crinone® 8% once daily	Total
Initial enrollment:				
Total screened				1504
Total down-regulated				1349
Total ovarian stimulation				1322
Randomized for the Intent-to-treat (ITT) Cohort	404	404	403	1211
Did not undergo embryo transfer	12(3%)	14 (3%)	12(2%)	38 (3.1%)
Completed 10 weeks of treatment	147 (36%)	158 (39%)	160(40%)	465 (38.4%)
Prematurely discontinued study	245 (61%)	232 (57%)	233 (58%)	710 (58.6%)
Reasons for discontinuation				
No positive pregnancy test	201 (50%)	163 (40%)	184 (46%)	
Biochemical or clinical pregnancy only	32 (8%)	38 (9%)	29 (7%)	
Loss of pregnancy	8 (2%)	17 (4%)	11 (3%)	
Adverse event	1 (<1%)	7(2%)	1(<1%)	
Noncompliance	1 (<1%)	1(<1%)	3(1%)	
Other drugs for luteal support	0	3 (1%)	1 (<1%)	
Protocol violation	0	1 (<1%)	1 (<1%)	
Subject choice	0	1 (<1%)	1 (<1%)	
Lost to follow-up	0	1 (<1%)	1 (<1%)	
Other	2 (<1%)	2 (<1%)	2 (<1%)	

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Subject Accounting and Final Study Disposition, Tables 14.1.1.1 and 14.1.1.3, pages 126 and 152 of 7469.

A total of 1504 subjects were screened for the study, but only 1211 completed down-regulation and ovarian stimulation successfully and were randomized (80.5%).

The safety (and ITT) cohort consisted all 1211 randomized subjects who successfully completed down-regulation and ovarian stimulation and also received at least one dose of progesterone study medication prior to embryo transfer.

Subjects that prematurely discontinued after randomization were not replaced. A total of 710 of 1211 subjects (approximately 58.6%) were discontinued from the study prior to 10 weeks of progesterone therapy. The most common reason for withdrawal before completion of the total of 10 treatment weeks was “no positive pregnancy test” in 548 of 1211 randomized subjects (45.3%). Other reasons for subject withdrawal (as seen in Table

9) included: a total of 99 of 1211 subjects (8.2%) who had no evidence of advancement in pregnancy beyond a biochemical or clinical pregnancy, 38 of 1211 subjects (3.1%) who had failure to undergo embryo transfer and 36 of 1211 subjects (3.0%) with a loss of pregnancy (abortion/miscarriage/ectopic).

No safety concerns arise from the 8 of 1211 subjects (0.7%) excluded for adverse events from the ITT cohort in the three treatment groups.

In Study 2004-02, subjects were considered compliant if they missed no more than 2 days of study drug since the previous visit. Study compliance was calculated as the total number of inserts (or gel packets) divided by the number of inserts (or gel packets) prescribed for the study period x 100 for each group. Subject compliance with the treatment regimen was reported in 1167 of the 1211 subjects in the ITT group (approximately 96.4%), and within each treatment group was reported for all visits as 392 of 404 subjects (97%) in the Endometrin® twice daily group, 389 of 404 subjects (96%) in the Endometrin® three times daily group, and 386 of 403 subjects (96%) in Crinone® 8% gel once daily group, respectively.

Compliance with the dosing regimen was summarized by treatment group and overall in study 2004-02. For the three treatment groups, dosing compliance ranged from 96% to 97% at all visits. Five subjects, one in the Endometrin® twice daily group (Patient 018002) and one in the Endometrin® three times daily group (Patient 017007) and three in the Crinone® once daily group (Patients 003077, 007024, 007038) were withdrawn from the study due to lack of compliance (from Sponsor's Data Listing 16.2.1.3).

Reviewer's comment: Because of their desire to have their therapy be successful and result in conception, infertility subjects are highly motivated to take medication as directed. In this reviewer's opinion, the small number of total subjects (5 of 1211 [0.4%]) removed for reasons of compliance does not appear to have had a major impact on the results of Study 2004-02, even slightly more subjects were removed (3 subjects from the Crinone® treatment group) as compared to 1 subject in each Endometrin® treatment arms.

6.1.4.4 Primary Efficacy Analysis – Ongoing Pregnancy Rate

The primary efficacy variable was ongoing pregnancy, defined as identification of fetal heart movement on transvaginal ultrasound at approximately 6 weeks of gestation (6 weeks post-embryo transfer). The primary efficacy analysis was performed to determine whether the ongoing pregnancy rate for each of the two dosing regimes of Endometrin® was non-inferior to Crinone®. The analysis compared the 95% confidence interval for the ongoing pregnancy rate for each treatment group separately. The analysis was performed using a step-down approach to assess the efficacy of the two Endometrin® treatment groups (100 mg twice daily and 100 mg three times daily). The Sponsor stated that Endometrin® 100 mg three times daily would be compared to Crinone® as the primary comparison. If the lower bound of the confidence interval for ongoing pregnancy rate

excluded a difference of greater than 10% in favor of Crinone®, then the non-inferiority of Endometrin® 100 mg twice daily was assessed. Therefore, with the step-down approach, no adjustment in the primary efficacy analysis was necessary to evaluate two dosing regimens. Non-inferiority was determined when the lower bound of the confidence interval excluded a difference of greater than 10% in favor of the comparator.

A summary of the ongoing pregnancy rates for the ITT population in the three treatment groups is seen in Table 10:

Table 10: Ongoing pregnancy rates per retrieval for the ITT population

Ongoing pregnancy	Endometrin® 100mg BID	Endometrin® 100 mg TID	Crinone® 8% once daily
N	404	404	403
Ongoing pregnancy rate n (%)	156 (39%)	171 (42%)	170 (42%)
95% Confidence Interval (CI)	[33.8,43.6]	[37.5,47.3]	[37.3,47.2]
Difference between Endometrin® and Crinone®	-3.6%	0.1%	
[95% CI lower bound for difference]	[-10.3]	[-6.7]	

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 15, page 62 of 7469.

Both Endometrin® treatment groups met the predetermined 10% non-inferiority limit to establish non-inferiority to Crinone® in the ITT population.

Reviewer's comment: Table 10 shows that Endometrin® two times and three times daily treatment groups met the 10% non-inferiority criterion that was outlined in the protocol prior to the start of Study 2004-02. In addition, the reviewer agrees for the ITT population that there were no clinically meaningful differences in ongoing pregnancy rates between the Endometrin® treatment group and the Crinone® treatment groups. The proposed protocol does not include primary or secondary efficacy comparisons between the two Endometrin® treatment groups to each other.

6.1.4.4.1 Additional Analyses Submitted by the Sponsor

The Sponsor provided additional analyses of the impact of age and ovarian reserve on the response to progesterone treatment in terms of ongoing pregnancy rate. The Sponsor randomized and stratified Study 2004-02 for age and ovarian reserve (serum FSH level) as requested by the Division in an Advice letter dated October 22, 2004, but did not power as the Agency had suggested. The Sponsor reported that they selected the age groups for stratification based on matching the Society for Assisted Reproductive Technology database (SART 2002). The results of these secondary analyses by the Sponsor are seen in Table 11:

Table 11: Ongoing pregnancy rates in age and ovarian reserve defined subgroups (Sponsor's)

Ongoing pregnancy per retrieval	Endometrin® 100mg BID (ITT N=404)	Endometrin® 100 mg TID (ITT N=404)	Crinone® 8% once daily (ITT N=403)
Subjects < 35 years old (N)	247	247	243
Ongoing pregnancy rate n (%)	111 (44.9%)	117 (47.4%)	108 (44.4%)
95% Confidence Interval (CI)	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference between Endometrin® and Crinone®	0.5%	2.9%	
95% CI lower bound for difference	[-8.3%]	[-5.9]	
Subjects 35 – 37 years old (N)	89	93	98
Ongoing pregnancy rate n (%)	27 (30.3%)	37 (39.8%)	41 (41.8%)
95% Confidence Interval (CI)	[21.0, 41.0]	[29.8, 50.5]	[31.9, 52.2]
Difference between Endometrin® and Crinone®	-11.5%	-2.1%	
95% CI lower bound for difference	[-25.2]	[-16.0]	
Subjects 38-40 years old (N)	55	46	53
Ongoing pregnancy rate n (%)	16 (29.1%)	12 (26.1%)	16 (30.2%)
95% Confidence Interval (CI)	[17.6, 42.9]	[14.3, 41.1]	[18.3, 44.3]
Difference between Endometrin® and Crinone®	-1.1%	-4.1%	
95% CI lower bound for difference	[-18.3]	[-21.8]	
Subjects 41-42 years old (N)	13	18	9
Ongoing pregnancy rate n (%)	2 (15.4%)	5 (27.8%)	5 (55.6%)
95% Confidence Interval (CI)	[1.9, 45.4]	[9.7, 53.5]	[21.2, 86.3]
Difference between Endometrin® and Crinone®	-40.2%	-27.8%	
95% CI lower bound for difference	[-78.1]	[-66.3]	
Subjects with FSH < 10 IU/L (N)	350	347	350
Ongoing pregnancy rate n (%)	140 (40.0%)	150 (43.2%)	147 (42.0)
95% Confidence Interval (CI)	[34.8, 45.3]	[37.9, 48.6]	[36.8, 47.4]
Difference with Crinone®	-2.0%	1.2%	
[95% CI lower bound]	[-9.3]	[-6.1]	
Subjects with FSH 10-15 IU/L (N)	46	51	49
Ongoing pregnancy rate n (%)	16 (34.8%)	20 (39.2%)	23(46.9%)
95% Confidence Interval (CI)	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
Difference with Crinone®	-12.2%	-7.7%	
[95% CI lower bound]	[-31.8]	[-27.1]	

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.2.2.2 and 14.2.2.3, page 190 - 192 of 7469.

Reviewer's comments:

1. The Sponsor noted that for the subgroups < 35 years of age and FSH < 10 IU/L that the lower bounds of the 95% confidence interval for the difference in ongoing pregnancy rates demonstrated that both Endometrin® regimes were non-inferior to Crinone®. In this healthy population, it does not appear that there are any clinically significant differences between the treatment groups.
2. In subjects ≥ 35 years of age, and/or subjects with poor ovarian reserve (defined by the Sponsor as an FSH > 10 IU/L), the ongoing pregnancy rates were statistically and clinically lower in the Endometrin® groups as compared to the Crinone® group. The reviewer and the statistical reviewer re-categorized the groups to look at the entire subset of 35 and older age group as seen in Table 12:

Table 12: Ongoing pregnancy rate in age and ovarian reserve-defined subgroups (Division's)

Ongoing pregnancy in subgroups per retrieval	Endometrin® 100 mg BID N=404	Endometrin 100 mg TID N=404	Crinone® 8% once daily N=403
Subjects < 35 years of age (N)	247	247	243
Ongoing pregnancy rate n (%)	111 (44.9%)	117 (47.3%)	108 (44.4%)
95% Confidence Interval (CI)	[38.6, 51.4]	[41.0, 53.8]	[38.1, 50.9]
Difference with Crinone®	0.5%	2.9%	--
[95% CI for difference]	[-8.3, 9.3]	[-5.9, 11.7]	--
Subjects 35-42 years of age (N)	157	157	160
Ongoing pregnancy rate n (%)	45 (28.7%)	54 (34.4%)	62 (38.8%)
95% Confidence Interval (CI)	[21.7, 36.4]	[27.0, 42.4]	[31.2, 46.8]
Difference with Crinone®	-10.1%	-4.4%	--
[95% CI for difference]	[-20.3, 0.3]	[-14.9, 6.3]	--
Subjects with FSH < 10 IU/L (N)	350	347	350
Ongoing pregnancy rate n (%)	140 (40.0%)	150 (43.2%)	147 (42.0)
95% Confidence Interval (CI)	[34.8, 45.3]	[37.9, 48.6]	[36.9, 47.4]
Difference with Crinone®	-2.0%	1.2%	--
[95% CI for difference]	[-9.3, 5.3]	[-6.1, 8.5]	--
Subjects FSH 10-15 IU/L (N)	46	51	49
Ongoing pregnancy rate n (%)	16 (34.8%)	20 (39.2%)	23 (46.9%)
95% Confidence Interval (CI)	[21.4, 50.2]	[25.8, 53.9]	[32.5, 61.7]
Difference with Crinone®	-12.2%	-7.7%	--
[95% CI for difference]	[-31.0, 7.7]	[-26.6, 11.6]	--

Based on this information, the reviewer has significant concerns that in the 35 and older age group and in those with a serum FSH of 10 IU/L or greater, neither of the Endometrin doses was efficacious compared to Crinone® but the prespecified -10%

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criteria used for the ITT population. The DOSAGE AND ADMINISTRATION section of the label should reflect this lack of information.

In addition, the Sponsor also examined the effects on ongoing pregnancy rate comparing: type of insemination (in vitro fertilization [IVF] compared to intracytoplasmic injection [ICSI], use of assisted hatching and day of transfer across the three treatment groups as seen in Table 13:

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On Original**

Table 13: Ongoing pregnancy rates per retrieval sub grouped by methodology of ART

Ongoing pregnancy	Endometrin® 100mg BID ITT N=404	Endometrin® 100 mg TID ITT N=404	Crinone® 8% once daily ITT N=403
ICSI (N)	287	278	299
Subjects with an ongoing pregnancy n (%)	105 (37%)	117 (42%)	129 (43%)
95% Confidence Interval (CI)	[31.0,42.4]	[36.2, 48.1]	[37.5,49.0]
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	-6.7% [-14.6]	-1.1 [-9.1]	
IVF (N)	116	123	99
Subjects with an ongoing pregnancy n (%)	51 (44%)	54 (44%)	41 (41%)
95% Confidence Interval (CI)	[34.8, 53.5]	[35.0, 53.1]	[31.6, 51.8]
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	2.6% [-10.7]	2.5% [-10.6]	
Assisted Hatching			
Yes (N)	161	166	163
Ongoing pregnancy rate n (%)	64(40%)	70(42%)	61(37%)
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	2.3% [8.3]	4.7% [-5.8]	
No (N)	241	235	235
Ongoing pregnancy rate n(%)	92(38%)	101(43%)	109(46%)
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	-8.2% [17.1]	-3.4% [12.4]	
Day of Embryo transfer			
Day 3 (N)	241	236	225
Ongoing pregnancy rate n (%)	95(39%)	108(46%)	80(36%)
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	3.9% [-4.9]	10.2% [1.3]	
Day 5 (N)	127	126	133
Ongoing pregnancy rate n (%)	54(43%)	55(44%)	75(56%)
Difference between Endometrin® and Crinone® [95% CI lower bound for difference]	-13.9% [25.9]	-12.7% [-24.8]	

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 17 and 20, pages 65 and 68, respectively, of 7469.

The Sponsor stated that the ongoing pregnancy rates when evaluated by type of insemination were similar across the three treatment groups.

Reviewer's comments:

- The Sponsor did not stratify the randomization in Study 2004-02 by insemination type as requested in the Division's October 2004 Advice letter. However, the reviewer agrees with the Sponsor that in general, across the treatment groups, the numbers of subjects having IVF compared to ICSI was similar across treatment*

groups, with ICSI occurring at roughly twice the rate of IVF. From a clinical perspective, the pregnancy rates for IVF appear similar across the treatment groups for Endometrin® three times daily and Crinone®. It is unclear to the reviewer why the rates for Endometrin® twice daily with ICSI are clinically lower than Endometrin® three times daily or Crinone®.

2. The Endometrin® and Crinone® treatment groups with or without Assisted Hatching appear to be clinically and statistically similar.
3. Overall pregnancy rates are higher for all three treatment groups with Day 5 transfer. However, it is unclear to the reviewer why the two Endometrin® treatment groups did worse than Crinone® with use of Day 5 transfer, and better than Crinone® with use of Day 3 transfer. These clinical differences may actually reflect pharmacokinetic differences between Endometrin® and Crinone®, although the study was not powered to evaluate subjects specifically for the variable of embryo transfer.

Subjects in Study 2004-02 were also evaluated by body as recommended by the Division in an Advice letter dated October 22, 2004 and reiterated at the EOP2 meeting on February 28, 2005 as shown in Table 14:

Table 14: Sponsor's ongoing pregnancy rates per retrieval stratified by body weight

Ongoing pregnancy	Endometrin® 100mg BID N=404	Endometrin® 100 mg TID N=404	Crinone® 8% once daily N=403
Total subjects - BMI < 18.5 kg/m ² (N)	6	10	10
Ongoing pregnancy n (%)	3 (50%)	8 (80%)	3 (30%)
95% Confidence Interval (CI)	[11.8, 88.2]	[44.4, 97.5]	[6.7, 65.2]
Difference with Crinone®	20%	50.0%	
[95% CI lower bound]	[-29.1]%	[12.3]	
Total subjects - BMI 18.5 to 24.9 kg/m ² (N)	209	199	214
Ongoing pregnancy n (%)	88 (42%)	84 (42%)	99 (46%)
95% Confidence Interval (CI)	[35.3, 49.1]	[35.3, 49.4]	[39.4, 53.2]
Difference with Crinone®	-4.2%	-4.1%	
[95% CI lower bound]	[13.6]	[-13.6]	
Total subjects - BMI 25.0 to 29.0 kg/m ² (N)	121	120	112
Ongoing pregnancy n (%)	42 (35%)	53 (44%)	45 (40%)
95% Confidence Interval (CI)	[26.3, 43.9]	[35.1, 53.5]	[31.0, 49.9]
Difference with Crinone®	-5.5%	4.0%	
[95% CI lower bound]	[-17.9]	[-8.7]	
Total subjects - BMI ≥ 30 kg/m ² (N)	66	75	66
Ongoing pregnancy n (%)	23 (35%)	26 (35%)	23 (35%)
95% Confidence Interval (CI)	[23.5, 47.6]	[24.0, 46.5]	[23.5, 47.6]
Difference with Crinone®	0.0%	-0.2%	
[95% CI lower bound]	[-16.3]	[-15.9]	

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 19, page 67 of 7469.

Reviewer's comment: From a clinical view, no clinical differences were seen between the groups when sub-grouped by body mass index. In addition, the numbers of subjects in the very low (< 18.5 kg/m²) sub-group was too small to make any conclusions on ongoing pregnancy. However it the reviewer is reassured that in subjects with a high body mass index group (≥ 30 kg/m²), as is seen in many pre-menopausal women in the US, there do not appear to be clinical differences in ongoing pregnancy between the treatment groups.

6.1.5 Clinical Microbiology

This section is not applicable as this is not an antimicrobial product.

6.1.6 Efficacy Conclusions

The results from the primary, phase 3 Study 2004-02 demonstrated that:

- The results from the Endometrin® group administered the twice daily regimen met the pre-specified analysis for non-inferiority with criterion (10%) relative to the comparator (Crinone®) based on the lower bound of the 95% confidence interval for the overall ITT population for ongoing pregnancy (defined by the Sponsor as identification of fetal heart motion at approximately 6 weeks of gestation).
- The results from the Endometrin® group administered three times daily met the pre-specified analysis for non-inferiority criterion (10%) relative to the comparator (Crinone®) based on the lower bound of the 95% confidence interval for the overall ITT population for ongoing pregnancy (defined by the Sponsor as identification of fetal heart motion at approximately 6 weeks of gestation).
- Preplanned and pre-specified sub-group analyses of subjects by age and ovarian reserve appears to demonstrate that in subjects ≥35 and with poor ovarian reserve (defined by an FSH > 10 IU/L), the pre-specified non-inferiority criterion limit (-10%) on the lower bound of the 95% confidence interval was not met when the group administered Endometrin® twice daily and the group administered Endometrin® three times daily were compared to Crinone®. This information and the implication to patients falling in the age greater than or equal to 35 sub-group and the sub-group defined by FSH greater than 10 IU/L should be clearly discussed in the Endometrin® label.

Reviewer's comment: The Sponsor requested labeling on the clinical choice between the dosage regimens as follows, "Endometrin® is a tablet that is administered vaginally at a dose of 100 mg two or three times daily in women who require progesterone supplementation as part of Assisted Reproductive Technology (ART)." ∟

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7.1 Methods and Findings

In phase 3 Study 2004-02, a total of 1211 subjects who completed down-regulation and ovarian stimulation were randomized to one of three progesterone treatment groups. These groups included:

- 404 subjects on 100 mg of Endometrin® twice daily,
- 404 subjects on 100 mg of Endometrin® three times daily, and
- 403 subjects on Crinone® 8% gel once daily.

The treatment period for luteal supplementation with progesterone (Endometrin® inserts or Crinone® gel) in Study 2004-02 was 10 total weeks. Luteal supplementation was preceded by down-regulation with gonadotropin-releasing hormone agonist, ovarian stimulation and oocyte retrieval. Subjects were started on a daily progesterone regimen (Endometrin® inserts twice daily, Endometrin® inserts three times daily or Crinone® once daily) the day after oocyte retrieval.

In the primary phase 3 Study 2004-02, additional safety was also assessed by comparison of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), standard laboratory test results, transvaginal ultrasound, and vital signs at visits scheduled at baseline and during the 10 week treatment period (or early termination).

In the two phase 1 studies, the safety of Endometrin® was evaluated including: vital signs that were monitored during the study, electrocardiograms that were obtained at study entry and completion, and adverse events that were monitored throughout the multiple-dose study.

Safety evaluations included:

- 2004-01 (Multiple dose study of different dosages and regimens of Endometrin® compared to a group treated with injectable progesterone over a 10-day treatment period) – A total of 58 subjects were included in the safety analysis. Study 2004-01 also included endometrial assessment (including transvaginal ultrasound and endometrial biopsies) and colposcopy performed at screening and at completion of the 10-day treatment.
- 2005-08 (Multiple dose study of the two planned Endometrin® dosing regimens for phase 3 over a 6-day treatment period) – A total of 18 subjects in this study were included in the safety analysis

Adverse events (AEs) for the primary phase 3 Study (2004-02) and the two pharmacokinetic studies (2004-01 and 2005-08) were reported during the regularly scheduled visits to the investigational site in both studies. Site personnel recorded the information regarding each event on the AE page of the Case Report Form (CRF).

No unexpected safety issues in any of the three studies that were evaluated were identified during this review of NDA 22-057/S-000.

7.1.1 Deaths

No deaths occurred during or following the conduct of primary, phase 3 Study 2004-01 or in the two phase 1 Studies (2004-01 and 2005-08) conducted by the Sponsor.

7.1.2 Other Serious Adverse Events

One thousand two hundred and eleven (1211) subjects were randomized to receive one of the three treatments in Study 2004-02 and were considered the safety population. A total of 31 subjects reported serious adverse events for Study 2004-02. Table 15 summarizes the serious adverse events reported in Study 2004-02.

Table 15: Serious Adverse Events (Safety Cohort) for Study 2004-02

Body System MedDRA preferred term	Endometrin 100 mg twice daily N=404	Endometrin 100 mg three times daily N=404	Crinone 8% gel once daily N=403
Subjects with ≥ 1 Serious Adverse Event	14 (3%)	8 (2%)	9 (2%)
Gastrointestinal Disorders	2 (<1%)	0	1 (<1%)
Abdominal pain	1 (<1%)	0	0
Abdominal pain upper	1 (<1%)	0	0
Ascites	0	0	1 (<1%)
Infections and Infestations	0	1 (<1%)	0
Postoperative Infection	0	1 (<1%)	0
Neoplasms Benign, Malignant and Unspecified	1 (<1%)	0	0
Thyroid gland cancer	1 (<1%)	0	0
Pregnancy, Puerperium and Perinatal Conditions	1 (<1%)	1 (<1%)	3 (1%)
Abortion threatened	0	1 (<1%)	0
Ectopic pregnancy (all)	1 (<1%)	0	2 (<1%)
Placenta praevia	0	0	1 (<1%)
Reproductive System and Breast Disorders	9 (2%)	6 (1%)	6 (1%)
Ovarian hyperstimulation syndrome	7 (2%)	6 (1%)	6 (1%)
Ovarian torsion	2 (<1%)	0	0
Vascular disorders	1 (<1%)	0	0
Deep vein thrombosis	1 (<1%)	0	0

Sources: Adapted from NDA 22-057/000, Final Report for Study 2004-02, Table 37, page 91 of 7469

Summaries of the serious adverse events include:

- a. **Endometrin® 100 mg insert twice daily group:** Fourteen (14) SAEs were reported in 14 subjects (3% of 404). These SAEs are summarized below:
 - Nonreproductive SAEs (4 subjects) in the Endometrin® twice daily group:
 - Deep venous thrombosis: Subject 007017 was a 38 year old female with no history of coagulopathy who underwent down-regulation with Yasmin® oral contraception and leuprolide acetate. She had ovarian stimulation with Bravelle® and Menopur® and was given human chorionic gonadotropin prior to oocyte retrieval. Oocytes were retrieved and she was started on Endometrin® twice daily. Subsequent to retrieval, she underwent a Day 3 embryo transfer of 3 embryos. Pregnancy was confirmed two weeks later in August 2005. On

_____ she was hit in the right leg by a volleyball, and her leg became painful and swollen. She was seen in an urgent care facility and told she had superficial phlebitis and was discharged. Two days later, _____ she was seen by her obstetrician with continued complaints of pain and determined to have significant varicose veins of the lower extremity. A Doppler of the lower extremity showed a blood clot in the popliteal vein and she was admitted to the hospital for 5 days for heparin therapy. She continued on heparin as an outpatient for the remainder of the pregnancy and was diagnosed with Factor V Leiden disorder.

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- Thyroid cancer: Subject 0017035 was a 24 year old female who underwent down-regulation with leuprolide acetate. She had ovarian stimulation with Bravelle® and Menopur® and was given human chorionic gonadotropin prior to oocyte retrieval. Oocytes were retrieved and she was started on Endometrin® twice daily. Endometrin® use was discontinued 14 days later when she was found not to be pregnant. At the time of the exit visit, she was found to have an enlarged thyroid and was sent for evaluation. The subject called 3 months later to inform the investigator that she had been diagnosed with thyroid cancer and had undergone a complete thyroidectomy for well differentiated papillary carcinoma with the surgical margins free of cancer.
- Cholecystitis: Subject 026058 was a 26 year old female who underwent down-regulation with leuprolide acetate. She had ovarian stimulation with Bravelle® and Menopur® and was given human chorionic gonadotropin prior to oocyte retrieval. Oocytes were retrieved and she was started on Endometrin® twice daily. She underwent embryo transfer, and two weeks later, she was found to be pregnant. Approximately one month later, she presented to the emergency room with epigastric pain and vomiting, she underwent obstetrical testing and was found to have a twin intrauterine pregnancy. Ultrasound of the gallbladder revealed a 1.2 cm gallstone in the neck of the gallbladder. A laparoscopic cholecystectomy was performed without complication, and the abdominal complaints resolved.
- Abdominal pain (etiology unclear admitted twice as an in-patient): Subject 019150 was a 29 year old female who underwent down-regulation with leuprolide acetate. She had ovarian stimulation with Bravelle® and Menopur® and was given human chorionic gonadotropin prior to oocyte retrieval. Oocytes were retrieved and she was started on Endometrin® twice daily. She underwent embryo transfer, and two weeks later, she was found to be pregnant with twins. Approximately one month later, she complained of lower abdominal pain, nausea and vomiting and was admitted to the hospital overnight. She was hydrated, treated with pain medication and released. She was

readmitted four days later (3/5) for abdominal pain and was treated for a urinary tract infection and for constipation. No clear etiology was ever identified for the abdominal pain.

- Reproductive and pregnancy SAEs (11 subjects) in the Endometrin® twice daily group:
 - Ovarian hyperstimulation syndrome (OHSS): Seven subjects (002020, 003009, 012049, 014014, 015018, 020002, 023008) were diagnosed with OHSS as a serious adverse event while using Endometrin®. OHSS is a known result of ovarian stimulation with gonadotropins and human chorionic gonadotropin use and not progesterone use.
 - Ovarian torsion: Two subjects (003049 and 009012) were diagnosed with ovarian torsion. These two subjects had leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Endometrin® twice daily, these two subjects had embryo transfer, and subsequently conceived twin pregnancies.
 - Subject 003049 had a concomitant 10 cm hemorrhagic ovarian cyst removed during a salpingoopherectomy, and had an unremarkable recovery.
 - Subject 009012 had an episode of right lower quadrant pain and then was evaluated by an ultrasound that confirmed pregnancy but showed no blood flow to the right ovary by Doppler study. She underwent laparoscopic oopherectomy and was discharged home. Approximately three weeks later the subject again complained of pain and was found to have no blood flow on the left ovary by Doppler study, and a salpingectomy on the opposite adnexa was performed. She was discharged with an ongoing twin pregnancy.
 - Ectopic pregnancy: One subject (024027) was diagnosed with an ectopic pregnancy. This subject had leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Endometrin® twice daily, this subject had embryo transfer, and was then determined to have a positive pregnancy test. On ultrasound, this subject was diagnosed with a left ectopic pregnancy, which was then surgically removed.
- b. **Endometrin® 100 mg insert three times daily group:** 8 SAEs in 8 subjects (8 of 404 [2%] are summarized below:
 - Nonreproductive SAEs in the Endometrin® three times daily group:
 - None reported
 - Reproductive SAEs in the Endometrin® three times daily group
 - Ovarian hyperstimulation syndrome (OHSS): Six subjects (007085, 011007, 15009, 16007, 17030 and 020029) were diagnosed with OHSS as a serious adverse event while using Endometrin®. OHSS is a

- known result of ovarian stimulation with gonadotropins and human chorionic gonadotropin use and not progesterone use.
- Postoperative complication: Subject 014050 had a complication of a dilation and curettage (D&C) for a missed abortion. This subject underwent leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Endometrin® three times daily, this subject had embryo transfer, and was determined to have a positive pregnancy test. Her ultrasound at 6 weeks noted a twin intrauterine pregnancy. However, approximately 1 month later, another ultrasound revealed no fetal activity in either fetus, and she underwent a D&C. On post-operative day 1, the subject developed fever and pain and was taken to the operating room for an exploratory laparotomy where she had a left salpingoopherectomy, a right salpingectomy and repair of bowel serosa.
 - Threatened abortion (Subchorionic hematoma during pregnancy): One subject (005048) had a confirmed diagnosis of a diamniotic gestation. This subject had leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Endometrin® three times daily, this subject had embryo transfer, and subsequently had a dichorionic twin pregnancy. Subject had vaginal spotting and was diagnosed with a small subchorionic hematoma. She was hospitalized for 3 days for vaginal bleeding, however, the bleeding resolved and she completed her 10-week treatment period with Endometrin® and study exit visit.
- c. Crinone® 8% gel once daily treatment group: 9 SAEs in 9 subjects (9 of 403 [2%] are summarized below:
- Nonreproductive SAEs in the Crinone® once daily group:
 - None reported
 - Reproductive SAEs in the Crinone® once daily group
 - Ovarian hyperstimulation syndrome (OHSS): Six subjects (005006, 005022, 005097 (listed as ascites), 007038, 019037 and 024021) were diagnosed with OHSS while using Crinone® as a serious adverse event. Subject 005097 was also reported to have concomitant ascites concomitantly with OHSS.
 - Placenta previa: Subject 005030 had a viable triplet pregnancy, and a posterior placenta previa. This subject underwent leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Crinone® once daily, this subject had embryo transfer, and was determined to have a positive pregnancy test. Her ultrasound reported a triplet intrauterine pregnancy. She had an episode of vaginal bleeding and was admitted to the hospital for 3 days and sent home on bedrest. The subject completed her Crinone® treatment, and her study exit visit.

- Ectopic pregnancy: Two subjects (007028 and 0019092) were diagnosed with an ectopic pregnancy. These two subjects had successful leuprolide down-regulation, ovarian stimulation and oocyte retrieval. After initiating Crinone® once daily, both subjects had embryo transfer, and subsequently became pregnant. Both subjects had ectopic pregnancy required surgical removal.

Reviewer's comment: The 31 serious adverse events in Study 2004-02 were evaluated both individually and by site. The reviewer agrees with the Sponsor that the majority were unrelated to progesterone use (Endometrin® or Crinone®), and that the occurrence of these events did not appear to be limited to any specific investigational site. However, the reviewer notes that it is possible that progesterone (whether Endometrin® or Crinone®) could have contributed to the occurrence of venous thrombosis and cholelithiasis, but the actual increase in risk is unknown and cannot be determined from this information.

There were no serious adverse events reported in the two phase 1 studies (2004-01 and 2005-08).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

Table 16 shows the summary of subject disposition in phase 3 Study 2004-02. Overall, there was no clinical difference noted between groups in the number of subjects who dropout for pregnancy loss or adverse events.

Table 16: Summary of Subject Disposition in Study 2004-02

	Endometrin® 100 mg twice daily	Endometrin® 100 mg three times daily	Crinone® 8% gel once daily	Total
Randomized	404	404	403	1211
Completed 10-weeks of luteal supplementation with ongoing pregnancy	147 (36%)	158 (39%)	160 (40%)	465 (38%)
Discontinued for safety reasons for:				
Loss of pregnancy (miscarriage/abortion/ectopic)	8 (2%)	17 (4%)	11 (3%)	36 (3%)
Adverse event	2 (<1%)	7 (2%)	1(<1%)	10 (<1%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 6, page 50 of 7469.

Reviewer's comment: From a clinical perspective, the rates of discontinuation for pregnancy loss and discontinuation for adverse events appear to be similar between the treatment groups.

In the two pharmacokinetic studies (2004-01 and 2005-08), only one subject (1 of 58 [1.7%]) was discontinued from Study 2004-01 (for an adverse event) and there were no subjects that discontinued from Study 2005-08.

Reviewer's comment: The two pharmacokinetic studies were limited in the number of subjects who received progesterone (76 subjects) and the short exposure to Endometrin®. Therefore, no conclusions on discontinuation rates with Endometrin® can be made from these two phase 1 studies.

7.1.3.2 Adverse Events Associated with Dropouts

In the phase 3 Study 2004-02, 9 of 808 subjects in the two Endometrin® treatment arms discontinued due to one or more adverse events. Table 17 provides a description of the precipitating adverse event that resulted in discontinuation for all three treatment arms in Study 2004-02.

Table 17: Adverse Events Leading to Study Discontinuation for Study 2004-02

<u>Site #/Patient #</u>	<u>Treatment Group</u>	<u>MedDRA Coded Term</u>
003/037	Endometrin® 100 mg twice daily	Elevated Temperature
009/012*	Endometrin® 100 mg twice daily	Ovarian torsion
002/022	Endometrin® 100 mg three times daily	Dysuria/urethral irritation
002/044	Endometrin® 100 mg three times daily	Rash
003/029	Endometrin® 100 mg three times daily	Urticaria/peripheral edema
005/074	Endometrin® 100 mg three times daily	Vaginal bleeding/miscarriage
011/007*	Endometrin® 100 mg three times daily	OHSS†
017/030*	Endometrin® 100 mg three times daily	OHSS†
021/005	Endometrin® 100 mg three times daily	Rash
019/037*	Crinone® 8% vaginal gel once daily	OHSS†

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, pages 511 to 513 of 7469.

*Adverse event leading to discontinuation also documented as a Serious Adverse Event (SAE)

†(OHSS) Ovarian hyperstimulation syndrome

A brief summary of the adverse events leading to discontinuation as provided by the Sponsor from study 2004-02 that were probably unrelated to Endometrin® included:

➤ **Endometrin® 100 mg twice daily group:**

- Fever: Subject 003037 was a 27 year old who was randomized to the Endometrin® twice daily treatment group. This subject began Endometrin® prior to embryo transfer. However, the subject experienced an adverse event (an elevated temperature of 101.5°F) with a postnasal drip and cough. The investigator decided not to perform embryo transfer, and the study medication was discontinued. The reviewer agrees with the Sponsor that this elevated temperature was not likely to have been related to the study drug.

- Ovarian torsion: Subject 009012 was a 35 year old who was randomized to Endometrin® twice daily treatment group. This subject conceived after down-regulation, ovarian stimulation, oocyte retrieval and embryo transfer. She had bilateral ovarian torsion requiring bilateral oophorectomy. The investigator determined that since she had a viable pregnancy and no ovarian function, the subject required additional hormonal replacement and therefore this subject discontinued from Endometrin®. The reviewer agrees that the ovarian torsion was not likely to have been related to the study drug.
- **Endometrin® 100 mg three times daily group:**
 - OHSS: Subjects 011007 and 17030 were randomized to the Endometrin® three times daily treatment group and 019037 was randomized to the Crinone® daily group. This subject began progesterone supplementation prior to embryo transfer. However, these subjects developed ovarian hyperstimulation syndrome. The investigator decided not to perform embryo transfer on these subjects, and the study medication was discontinued. The reviewer agrees with the Sponsor that OHSS was not likely to have been related to the progesterone study drug (either Endometrin® or Crinone®).
 - Vaginal bleeding: Subject 005074 was a 29 year old female who was randomized to the Endometrin® three times daily group. Subject had successful down-regulation, ovarian stimulation and oocyte retrieval. Subject started Endometrin® and underwent embryo transfer. Subject had a positive pregnancy test and had a gestational sac on ultrasound. However, the subject began having mild bleeding and was diagnosed as having a missed abortion prior to completion of ten weeks of treatment.

Reviewer's comment: The reviewer agrees with the Sponsor that the missed abortion was not related to the Endometrin®, although it is important to note that Endometrin® did not appear to prevent the missed abortion from occurring.

Adverse events resulting in discontinuation possibly related to Endometrin® as summarized by the reviewer:

- **Endometrin® 100 mg three times daily:**
 - Dysuria: Subject 002022 was a 40 year old who was randomized to the Endometrin® three times daily treatment group. This subject had successful down-regulation, ovarian stimulation and oocyte retrieval. She began Endometrin® and underwent embryo transfer. Subject discontinued medication approximately 6 days later on October 15, 2006 because of dysuria and urethral irritation. A serum pregnancy test performed subsequently was negative three days later (on October 18, 2006). The reviewer agrees that the irritation was likely related to the study drug as the adverse event resolved after discontinuation of study drug.
 - Skin reactions: Three subjects 002044, 021105 and 003029 were randomized to the Endometrin® three times daily treatment group. The subjects had successful down-regulation, ovarian stimulation and oocyte retrieval. Both subjects began

Endometrin® and underwent embryo transfer. These two subjects both developed skin reactions that were considered related to Endometrin® (mild rash, moderate raised rash and urticaria, respectively). The reviewer agrees that given the timing of the skin reaction to administration of the study drug and that fact the skin reactions resolved after discontinuation of study drug, these reactions are likely related to Endometrin® use.

Reviewer's comment: From the data presented in Table 17, more subjects were discontinued in the 100 mg Endometrin® three times daily (7 subjects) as compared to the other two progesterone treatment groups (2 subjects) in the Endometrin® twice daily group and (one subject) in the Crinone® group (for ovarian hyperstimulation syndrome). In this reviewer's opinion, the most concerning adverse events that resulted in discontinuation were in the three subjects who had skin reactions (3 of 404 subjects, 0.7%) with use of Endometrin® three times daily. These subjects in the Endometrin® three times daily group could potentially be demonstrated a presumed to be allergic to progesterone or Endometrin®. In contrast, there were no skin reactions or rashes in the Endometrin® twice daily or Crinone® treatment groups. The reviewer has some concerns that the increased number of doses of Endometrin® may be related an increased risk of allergy. It is reassuring that all of these skin reactions were rated as mild to moderate reactions and none of the skin reactions were life-threatening or appeared to be anaphylactic reactions. However, based on these presumed findings of possible allergy to progesterone in some subjects, these type of events need to be addressed in labeling and monitored during post-marketing.

In the two pharmacokinetic studies (2004-01 and 2005-08), 1 subject in Study 2004-01 (1.7%, 1 of 58 randomized subjects) discontinued due to an adverse event and no subjects discontinued in Study 2005-08. Table 18 provides a description of the precipitating adverse event that resulted in study discontinuation.

Table 18: Adverse Events Leading to Study Discontinuation in Studies 2004-01 and 2005-08

<u>Study</u>	<u>Center/Patient #</u>	<u>Treatment Group</u>	<u>MedDRA Coded Term</u>	
2004-01	— /02058	Endometrin® twice daily	Left calf pain	b(4)

Adverse event resulting in discontinuation unlikely related to study drug:

- Subject 02058 was a 36 year old female who had bilateral varicose veins. This subject received down-regulation and complained of calf pain three days prior to randomization that was considered moderate. This subject received one dose of Endometrin® and was then withdrawn from study participation as a result of the calf pain. The calf pain was reported resolved approximately 1 month later, and was determined by the investigator to be unlikely to have been related to the drug. The reviewer concurs as the pain began before the initiation of study drug treatment.

Reviewer's comment: Given the small number of subjects in the pharmacokinetic studies and the limited time of exposure to Endometrin®, no definitive safety conclusions can be made based on the single discontinuation.

7.1.3.3 Other Significant Adverse Events

Other treatment-emergent adverse events that occurred in Study 2004-02 across the three treatment groups included: “postprocedural pain” (post-embryo transfer pain in 26.3%, 319 of 1211 subjects), “abdominal pain” (12.4%, 150 of 1211 subjects), “nausea” (7.8%, 92 of 1211 subjects) and ovarian hyperstimulation syndrome (6.8%, 83 of 1211 subjects). Across the three treatment groups:

- Postprocedural pain was reported in: 28% in 115 of 404 subjects in the Endometrin® twice daily group, 25% in 102 of 404 subjects in the Endometrin® three times daily group, and 25% in 102 of 403 subjects in the Crinone® treatment group.
- Abdominal pain was reported in: 11% or 43 of 404 subjects in the Endometrin® twice daily group, 11% or 45 of 404 subjects in the Endometrin® three times daily group and 15% or 62 of 403 subjects in the Crinone® treatment group.
- Nausea was reported in: 8% or 32 of 404 subjects in the Endometrin® twice daily group, 7% in 29 of 404 subjects in the Endometrin® three times daily group and 8% in 31 of 403 subjects in the Crinone® treatment group
- Ovarian hyperstimulation syndrome was reported in: 7% (30 of 404) of subjects in the Endometrin® twice daily group, 7% (27 of 404) of subjects in the Endometrin® three times daily group and 6% (26 of 403) of subjects in the Crinone® treatment group.

These treatment-emergent events appeared to be clinically similar in rates across the treatment groups, and the reviewer concurs with the Sponsor that no safety trends appear to be seen in these small numbers of adverse events.

One significant adverse event of interest with use of progesterone was vaginal bleeding (reported as the preferred term vaginal haemorrhage). The Sponsor reported that the rate of vaginal hemorrhage rate in all subjects in Study 2004-02 occurred in 32 of 1211 subjects (2.6%). All of the reports of vaginal hemorrhage were reported as mild or moderate, and none were reported as a serious adverse event. In the treatment groups, vaginal hemorrhage was reported in:

- 7 of 404 subjects (2%) in the Endometrin® twice daily group
- 9 of 404 subjects (2%) in the Endometrin® three times daily group
- 16 of 403 subjects (4%) in the Crinone® once daily group.

Reviewer's comments:

1. *Rates of the majority of these significant adverse events (including hyperstimulation) seen with subjects undergoing Assisted Reproductive Technology therapy do not raise any new safety concerns or trends. The reviewer does not believe that hyperstimulation and/or postprocedural pain rates or severity are likely to have been a result of progesterone use or dose.*
2. *The reviewer notes that the actual rate of vaginal bleeding may have been much higher than that calculated by the Sponsor. The Sponsor divided subjects by whether they had vaginal bleeding or vaginal spotting. Subjects with vaginal bleeding were listed as vaginal haemorrhage; those with spotting were listed as metrorrhagia. The reviewer*

evaluated all of these cases together as the reviewer could not determine how the investigators distinguished bleeding from spotting. Furthermore, if the spotting was listed first (spotting/bleeding), then the subject was listed as having metrorrhagia. If the subject had bleeding/spotting, then the subject was listed as vaginal haemorrhage. Therefore, the reviewer evaluated all subjects with any form of vaginal bleeding or spotting as a worst case scenario. Subjects with vaginal bleeding and/or spotting included:

- 13 of 404 subjects (3.2%) in the Endometrin® twice daily group
- 14 of 404 subjects (3.5%) in the Endometrin® three times daily group
- 23 of 403 subjects (5.7%) in the Crinone® once daily group

The reviewer notes that none of these bleeding events were serious or severe. In addition, none of these events were considered by the investigator to be related to treatment. The reviewer recognizes that pregnancy and dropping hormones in subjects who are not pregnant may contribute to bleeding and/or spotting. This reviewer concludes that vaginal bleeding as reported by subjects when comparing the two Endometrin® groups appears to be similar between the two Endometrin® treatment arms. In addition, both Endometrin® groups have lower overall bleeding rates than the Crinone® group. The reviewer has no explanation why the Crinone® group has a higher rate, given the similar ongoing pregnancy rates between groups.

Other treatment-emergent adverse events that were considered clinically significant in the two pharmacokinetics studies (2004-01 and 2005-08) included:

1. 2004-01 (multiple dose study) - 25 subjects (25 of 58 dosed subjects [43.1%]) reported a treatment emergent adverse event.
 - The most frequently reported (and considered clinically significant by the reviewer) adverse events (AE) were headache and dysmenorrhea, with each AE reported in 7 of 58 total subjects and 5 of 58 subjects, respectively (12.1% and 8.6%).
 - Headache was seen in: one subject (1 of 11 [9%]) in the 100 mg Endometrin® once daily group, one subject (1 of 9 [11 %]) in the 200 mg Endometrin® once daily group, two subjects (2 of 10 [20%]) in the 200 mg Endometrin® twice daily group and three subjects (3 of 10 [30%]) in the injectable progesterone in oil group.
 - Dysmenorrhea was seen in: one subject (1 of 11 [9%]) in the 100 mg Endometrin® once daily group, one subject (1 of 9 [11%]) in the 200 mg Endometrin® once daily group, two subjects (2 of 9 [22%]) in the 100 mg Endometrin® twice daily group and one subject (1 of 10 [10%]) in the injectable progesterone in oil group.
 - Clinically significant abnormal laboratory values were reported in 2 of 58 total subjects (3.5%) in this study. Subjects 02049 and 02046 after 10 days of progesterone therapy (Subject 02049 in the Endometrin® 50 mg daily group and Subject 02046 in the Endometrin® 200 mg twice daily group, respectively) were reported to have elevated liver function tests. Follow-up evaluation in both subjects revealed that the repeat laboratory values for both subjects returned to

within normal range. The Sponsor reported that the first subject's abnormal liver function tests were not related to study drug and the second subject's abnormal liver function had an uncertain relationship to the study drug.

2. 2005-08 (multiple dose study) –18 subjects reported 6 treatment emergent adverse events (6 of 18, 33.3%).
 - The most frequently reported adverse event was vaginal bleeding reported in 3 of the 6 total subjects (50%) in the Endometrin® 100 mg three times daily treatment group. All of these adverse events were reported as mild, and none were reported as serious adverse events.
 - No clinically meaningful changes in laboratory, vital signs or 12-Lead EKGs were noted by the Sponsor, and all subjects were reported to have normal EKG findings at baseline and post-treatment. The reviewer agrees with the Sponsor that none of the abnormal clinical values appear to be clinically significant.

Reviewer's comments:

1. *There were more subjects with mild vaginal bleeding in the Endometrin® three times daily group in Study 2005-08 than the other two treatment groups (Endometrin® twice daily and Crinone®). However, the reviewer considers Study 2005-08 too small to make any clinical conclusions about the rate of vaginal bleeding with use of Endometrin®. In addition, it is unclear whether the population treated in Study 2005-08 is comparable to those subjects treated with gonadotropins in Study 2004-02.*
2. *In this reviewer's opinion, the two subjects in Study 2004-01 with elevated enzyme elevations were unlikely to have these abnormal laboratories as a result of Endometrin® treatment. The reviewer agrees with the Sponsor that these liver function test elevations are more likely to have been a result of leuprolide acetate or transdermal estrogen treatments (as these drug products are known to result in transient increases in liver enzymes compared to progesterone products).*
3. *In this reviewer's opinion, no other significant adverse events, or laboratory abnormalities in the two phase 1 studies revealed any new safety concerns or trends for Endometrin® inserts. However, the reviewer notes that the safety data collected from these pharmacokinetic studies (2004-01 and 2005-08) is based on very short durations of exposure to progesterone and limited subject numbers. Therefore, in this reviewer's opinion, Study 2004-02 provides a better overview of the more clinically significant adverse events that will likely be seen with the proposed 10-week long exposure to Endometrin® for subjects who become pregnant after Assisted Reproductive Technologies and should be used in labeling.*

7.1.4 Other Search Strategies

There were no safety signals that arose from the studies conducted that required construction of any algorithm involving combination of clinical findings as a marker for a particular toxicity.