

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In Study 2004-02, adverse events (AEs) were reported during the subjects' regularly scheduled visits to the study centers including: Visit 1 (Screening visit and subsequent visits during post-screening for: down-regulation administration, confirmation of down-regulation and ovarian stimulation with gonadotropins), Visit 2 [Day of oocyte retrieval] and Visit 3 [14 days after post embryo transfer] for serum pregnancy testing. Visits 4, 5A and 5B occurred only if pregnancy was noted and progressing. Visit 4 [2 days after 1st positive serum pregnancy test] was to confirm initial pregnancy testing and Visit 5A [14 days after 2nd positive pregnancy test] to confirm on ultrasound presence of a gestational sac. Visit 5B [Week 15 or early termination]) was scheduled only for subjects with presence of at least one gestational sac at Visit 5A to confirm presence of an ongoing pregnancy with a fetal heart. At scheduled visits, center personnel conducted interviews to ascertain the occurrence of adverse events and recorded the information regarding each event on the AE page of the case report form (CRF). Similar recording procedures for adverse events were carried out in the pharmacokinetics studies (Studies 2004-01 and 2005-08).

The overall adverse event database was also examined across the investigational sites in the US as seen in Table 19:

Table 19: Adverse events by Sites that enrolled over 50 subjects

Site/Total subjects enrolled	Endometrin® 100 mg twice daily N=404	Endometrin® 100 mg three times daily N=404	Crinone® 8% gel once daily N=403
3/75	44	39	17
5/105	74	67	137
7/75	28	22	29
13/60	1	7	12
17/54	55	59	20
19/125	87	93	120
21/106	17	21	7
24/93	28	8	21
25/87	18	14	13
26/112	17	18	20

Reviewer's comments: The numbers of adverse events reported by these sites appears to be extremely variable. The reviewer notes that different physician practices, different protocols, or different patient populations could account for some of these differences in adverse event rates that were seen. However, it is also possible that not all adverse events were captured at some of the centers. Therefore, the reviewer will recommend that for future studies the Sponsor should make sure the investigators are educated on standardization of reporting all adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In the submission, the Sponsor reported the incidence of adverse events by MedDRA preferred term. While there may be many related terms that may be selected to describe an event in the MedDRA dictionary of preferred terms, there is no concern that the use of preferred terms resulted in a missed signal for the safety data from the Sponsor's studies (2004-02, 2004-01, and 2005-08 as reported in NDA 22-057/S-000.

7.1.5.3 Incidence of common adverse events

Phase 3 study (2004-01): Treatment-emergent adverse events (TEAE) were AEs that occurred on or after the first dose of study medication (Endometrin® or Crinone®) through the final study visit (including events that occurred after the last luteal treatment, but before the subject completed the study) were reported. A total of 1492 TEAEs across the three treatment groups in Study 2004-02 were reported by 53.0% (642 of 1211 subjects) of subjects in the safety cohort. The following Table 20 summarizes the adverse events reported:

Table 20: Study 2004-02 Treatment-Emergent Adverse Event Summary

Primary Safety Cohort	Endometrin® 100 mg twice daily N=404	Endometrin® 100 mg three times daily N=404	Crinone® 8% gel once daily N=403	Total N=1211
Subjects with at least one AE	215 (53%)	217 (54%)	210 (52%)	642 (53.0%)
Total number of AEs	495	461	536	1492
Subjects with SAE	14(3%)	8(2%)	9(2%)	31 (2.6%)
Subjects with an AE leading to discontinuation	2(<1%)	7(2%)	1(<1%)	9(0.7%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 36, page 90 of 7469.

Reviewer's comments:

1. Table 20 reveals similar adverse events across the three treatment groups. For common adverse events, the numbers of events and number of subjects with adverse events appeared to be similar between treatment groups.
2. No clinical difference is seen in discontinuations for serious adverse events between the three treatment groups (although the Endometrin® twice daily group had more SAEs, the additional SAEs noted do not appear directly related to Endometrin® therapy).
3. There are more discontinuations for an adverse event in the Endometrin® three times daily group compared to the other progesterone treatment groups. Of the seven discontinuations in the Endometrin® three times daily group, the three subjects (002044,

003029, and 021105) who had allergic-type reactions (Rash, urticaria with peripheral edema) that were of clinical concern (3 of 404, <1%).

4. The reviewer notes that in the original luteal replacement study for Crinone®, no subjects discontinued for an allergic-type reaction and in this study. However, the reviewer allergic-type reactions to progesterone products have been reported during post-marketing for both Crinone® and injectable progesterone products. In addition, the reviewer believes the lack of reporting of allergic reactions for Crinone® may have been a result of the small patient population studied (57 total subjects in the safety population (See Medical Officer's review of NDA 20-756 dated April 25, 1997. Based on the few serious allergic reactions with Endometrin®, and the lack of life-threatening reactions, the reviewer will recommend that the rates of allergic reactions for Endometrin® be monitored during initial post-marketing and that warnings be placed in the label.

Phase I studies (2004-01 and 2005-08): A total of 41 adverse events were reported during the two pharmacokinetic studies were reported by 40.8% (31 of 76 subjects) of in the pharmacokinetic safety cohort. The following Table 21 summarizes the all reported AEs that occurred during the two phase I studies (Studies 2004-01 and 2005-08).

Table 21: Pharmacokinetic Adverse Event Summary (Safety Cohort)

	2004-01 N=58	2005-08 N=18	Total N=76
Subjects with at least one AE	25	6	31
Total Number of AEs	34	7	41
Subjects with SAE	0	0	0
Subjects with AE Leading to Discontinuation	1	0	1

Sources: Adapted from NDA 22-057/S-000: Final Reports:

- Study 2004-01, Table 19, page 79 of 1625
- Study 2005-08, Table 13, page 60 of 857

Reviewer's comment: No safety conclusions can be made using the pharmacokinetic safety database for Studies 2004-01 and 2005-08 as the duration of Endometrin® use was limited. However, adverse events reported from the two pharmacokinetics studies seen in Table 21 do not demonstrate a new safety signal or trends.

7.1.5.4 Common adverse event tables

The following Table 22 shows the number (and percentage) of subjects reporting adverse events with $\geq 2\%$ occurrence for the three progesterone treatment groups in the primary efficacy and safety Study 2004-02. Findings from the two small phase I studies (2004-01 and 2005-08) were eliminated from this table as they studied a different subject population.

Table 22: Adverse Events with $\geq 2\%$ by Body System (Safety Cohort) in Study 2004-02

Body System Preferred Term	Endometrin® 100 mg BID* N=404	Endometrin® 100 mg TID** N=404	Crinone® 8% gel QD*** N=403
Number of patients with at least one AE n (%)	215 (53%)	217(54%)	210(52%)
Total number of AEs	495	461	536
Gastrointestinal disorders			
Abdominal pain (total)	50(12%)	50(12%)	62 (15%)
Nausea	32(8%)	29(7%)	31 (8%)
Abdominal distention	18(4%)	17(4%)	18 (4%)
Constipation	9(2%)	14 (3%)	16 (4%)
Vomiting	13(3%)	9 (2%)	5 (1%)
Dyspepsia	2(<1%)	4 (1%)	9 (2%)
General disorders and administration site conditions			
Fatigue	7(2%)	12(3%)	15(4%)
Infections and infestations			
Urinary tract infection	9(2%)	4(1%)	5(1%)
Vaginal mycosis	2(<1%)	4(1%)	10 (2%)
Injury, poisoning and procedural complications			
Postprocedural pain	115(28%)	102(25%)	102(25%)
Musculoskeletal and connective tissue disorders			
Back pain	6(1%)	4(1%)	5(1%)
Nervous system disorders			
Headache	15(4%)	13(3%)	18(4%)
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome	30(7%)	27(7%)	26(6%)
Uterine spasm	15(4%)	11(3%)	11(3%)
Vaginal bleeding (total)	13(3%)	14(3%)	16(4%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 37 pages 91 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

Reviewer's comment: This reviewer notes that there appeared to be some difficulty in differentiating between the etiologies of the categories of labeled Abdominal pain (general) from Abdominal pain (upper and lower) – so for the purposes of labeling – these categories were combined into the overall category of "Abdominal Pain". The reviewer had the same issue differentiating vaginal hemorrhage from metrorrhagia – so for labeling, these two categories were combined into a single "Vaginal bleeding" category.

The total number of subjects that reported at least one adverse event ($\geq 2\%$) was similar across the treatment groups with 215 of 404 subjects (53%) reporting at least one adverse event in the Endometrin® twice daily group, 217 of 404 subjects (54%) reporting at least one adverse event in the Endometrin® three times daily group, and 210 of 403 subjects (52%) reporting at least one adverse event in the Crinone® daily treatment group.

The most commonly reported nonreproductive AEs overall across the three active treatment regimens in order of occurrence ($\geq 2\%$) included: postprocedural pain (26.3%, 319 of 1211 subjects), abdominal pain (12.4%, 150 of 1211 subjects), and nausea (7.6%, 92 of 1211 subjects). The nonreproductive adverse events overall are similar between the Endometrin® treatment regimens and the Crinone® regimen with one clinical exception of note:

- Abdominal pain was slightly more common in subjects in the Crinone® treatment group (62 of 403 subjects, 15%) compared to the two other active Endometrin® 100 mg treatment groups (reported as 43 of 404 in the twice daily administration and 45 of 404 subject in the three times daily administration [approximately 11% of each treatment group] respectively).

In the reproductive system and breast disorders SOC, the most commonly reported non-reproductive AEs overall across the three active treatment regimens in order of occurrence ($\geq 2\%$) included:

- Ovarian hyperstimulation syndrome (6.9%, 83 of 1211 subjects)
- Uterine spasm (3.1%, 37 of 1211 subjects)
- Vaginal hemorrhage (2.6%, 32 of 1211 subjects).

Reviewer's comments:

1. Overall rates of TEAEs were clinically similar across the treatment groups. Specifically, reproductive and gastrointestinal disorders TEAEs were clinically similar across the three treatment groups. The reviewer concludes that the TEAEs seen support the conclusion that the safety of the two Endometrin® doses appear to be clinically similar to the comparator (Crinone®).
2. The adverse event information supplied by the Sponsor in the Adverse Event dataset (AE) was evaluated for vaginal bleeding and hemorrhage, a common occurrence of progesterone therapy. Out of the 32 subjects that reported vaginal bleeding in Study 2004-02, the reviewer observed that:
 - The number of subjects with vaginal bleeding was twice the number in the Crinone® group (16 subjects) compared to the other two Endometrin® groups (7 and 9 subjects, respectively).
 - In the Endometrin® treatment groups, most of the subjects who were reported to have vaginal bleeding were reported to have had mild bleeding (5 of 7 subjects in the Endometrin® twice daily group and 7 of 9 subjects in the Endometrin® three times daily group) by the site investigator. None of these vaginal bleeding adverse events were considered to have been a serious adverse event or resulted in discontinuation of progesterone treatment. Only one subject with moderate vaginal bleeding (25052) in the Endometrin® three times daily group required additional medical treatment for her vaginal bleeding, (although the subject's

hemoglobin appeared to have been unchanged during her treatment). In summary, from a clinical perspective, these episodes of vaginal bleeding appeared to be similar across the three treatment groups in terms of occurrence and severity.

Study 2004-01 (the first pharmacokinetic study): The most common adverse events seen across the Endometrin® treatment groups were headache and dysmenorrhea, each reported by a total of 4 subjects and nausea reported by a total of three subjects:

- Two subjects reported three severe adverse events in Study 2004-01: One subject [019009] in the 200 mg daily Endometrin® group had lipectomy and rhinoplasty during the study and one subject in the 200 mg twice daily Endometrin® group had muscle cramps. The Investigator determined that the severe adverse events were not related to the study drug and the reviewer concurs.
- Two subjects developed transient liver function tests on their Final Visit (Study Day 10). These subjects were previously summarized in section 7.1.3 and the reviewer concurs that these transient elevations in liver enzymes are probably unrelated to study drug

Study 2005-08 (the second pharmacokinetic study): The most common adverse events seen in the Endometrin® treatment groups was mild vaginal bleeding in three subjects in the Endometrin® three times daily group:

- Three subjects in the Endometrin® three times daily group had mild vaginal bleeding, and one subject each experienced abdominal pain, back pain, and rash on her forehead that resolved without treatment. The investigator reported that the vaginal bleeding occurred during the washout phase of single dose Endometrin® three times daily dosing, as was expected as this was probably progesterone withdrawal bleeding – the reviewer agrees.
- No adverse events were reported in the 6 subjects in the Endometrin® twice daily group

Reviewer's comment: Common adverse events in Studies 2004-01 and 2005-08 appear to be somewhat clinically similar to those AEs seen in 2004-02, although the patient population in 2004-01 and 2005-08 are very different (do not undergo additional medical and surgical therapy for Assisted Reproductive Technology). However, no new safety trends were seen in these small phase 1 studies, although the reviewer recommends that the adverse event information from these studies not be included in labeling, as these two pharmacokinetic studies were done in a different patient population from the primary efficacy and safety study.

7.1.5.5 Identifying common and drug-related adverse events

Per the submission, a total of 12 subjects of 1211 (<1%) had at least one treatment-emergent AE across the three treatment groups that were felt to be probably related to the study drug by the site investigators. The treatment-related AEs are listed in Table 23:

Table 23: Treatment-related adverse events in Study 2004-02

	Endometrin® 100 mg BID* N=404	Endometrin® 100 mg TID** N=404	Crinone® 8% gel QD*** N=403
MedDRA Preferred Term			
Total number of subjects with an AE considered probably related to study drug n (%)	4(<1%)	7(1.7%)	4(<1%)
General disorders and administration site conditions			
Peripheral edema	0	1(<1%)	0
Infections and infestations			
Fungal infection	0	1(<1%)	0
Reproductive system and breast disorders			
Genital pruritis female	1(<1%)	0	1(<1%)
Uterine inflammation	0	0	1(<1%)
Vaginal burning sensation	0	2 (<1%)	0
Vaginal pain	0	0	1(<1%)
Vulvovaginal discomfort	2 (<1%)	1(<1%)	0
Vulvovaginal dryness	1(<1%)	0	0
Skin and subcutaneous tissue disorders			
Pruritis	0	0	1(<1%)
Rash	0	1(<1%)	0
Urticaria	0	1(<1%)	0

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.3.1.4 page 433 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

Reviewer's comments: The treatment-related AE findings reported in Table 23 are not unexpected given the vaginal administration of Endometrin® and are clinically similar to Crinone® for these events. In this reviewer's opinion, the small number of treatment-related AEs does not show any new safety trends for progesterone products or Endometrin® use.

7.1.5.6 Additional analyses and explorations

The incidence of vaginal irritation and bleeding was a concern to the Division, given the presence of adipic acid in the final Endometrin® formulation. In the October 2004 Advice letter, the Division requested subjects record vaginal irritation and problems with intercourse during vaginal progesterone therapy during Study 2004-02.

The Sponsor used a diary card for subjects to monitor problems with sexual intercourse, vaginal irritation and vaginal bleeding. The summary of symptoms subjects were asked to report in the diary included:

- No intercourse
- No problems

- Vaginal pain
- Vaginal bleeding/spotting
- Other

The Sponsor summarized the presence of these symptoms recorded in the daily diary by treatment week. Approximately 35% of subjects completed cards at completion of progesterone therapy (week 10) The results of the symptoms of problems during sexual intercourse as recorded at baseline, week 5 (subjects that completed one-half of their progesterone treatment) and week 10 are seen in Table 24.

Table 24: Vaginal symptoms recorded on diary card (ITT population)

Symptom from diary card	Endometrin® 100 mg BID* (N=404)	Endometrin® 100 mg TID** (N=404)	Crinone® 8% gel QD*** (N=403)
Week 1	N=384	N=378	N=391
No intercourse	331 (86%)	331 (88%)	338 (86%)
No problems	22(6%)	20(5%)	26(7%)
Pain	6(2%)	7(2%)	3(1%)
Bleeding/spotting	0	0	0
Other	25(7%)	20(5%)	24(6%)
Week 5	N=161	N=174	N=172
No intercourse	99 (61%)	110 (63%)	111 (65%)
No problems	47(29%)	44(25%)	51(30%)
Pain	8(5%)	6(3%)	2(1%)
Bleeding/spotting	0	3(2%)	2(1%)
Other	7(4%)	11(6%)	6(3%)
Week 10	N=134	N=149	N=149
No intercourse	87 (65%)	99 (66%)	106 (71%)
No problems	41(31%)	39(26%)	39(26%)
Pain	1(1%)	5(3%)	0(0%)
Bleeding/spotting	1(1%)	1(1%)	1(1%)
Other	4(3%)	5(3%)	3(2%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 54, page 113 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

Reviewer’s comment: The reviewer notes that only 1/3 of enrolled subjects in the ITT population completed the symptom diary, and since subjects were not blinded, this information is descriptive. In addition, a majority of subjects in all three treatment groups did not have intercourse (65%, 66%, and 71%), and were therefore not evaluable. However, of the subjects who did report intercourse, 5% or less reported a problem (pain, bleeding/spotting or other) at Week 5, and 3% or less reported problems at Week 10.

Vaginal irritation was also evaluated through adverse event reporting at each clinic visit. Table 25 outlines vaginal complaints reported as adverse events in the ITT population:

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

Table 25: Vaginal irritation complaints reported as adverse events in Study 2004-02

MedDRA term	Endometrin® 100 mg BID* (N=404)	Endometrin® 100 mg TID** (N=404)	Crinone® 8% gel QD*** (N=403)
Vaginal burning sensation	0	3 (0.7%)	1(0.2%)
Vaginal pain	1(0.2%)	1(0.2%)	1(0.2%)
Vaginal irritation	2(0.5%)	1(0.2%)	1(0.2%)
Vaginal swelling	0	0	1(0.2%)
Vulvovaginal discomfort	3(0.7%)	1(0.2%)	1(0.2%)
Fungal infection/vaginal mycosis	3(0.7%)	5(1.2%)	10(2.5%)
Urinary tract infection	9(2.2%)	4(1.0%)	5(1.2%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.3.1.2 pages 262 and 257, respectively, of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

Reviewer's comment: Vaginal/vulvar complaints and infections appear to be clinically similar across the treatment arms. No reports of vaginal lesions or other reports of vaginal complaints were reported as serious adverse events, and only one subject discontinued because of urethral irritation (reported as mild by the subject with an uncertain relationship to the study drug by the Investigator) in the phase 3 study. Based on this vaginal AE information in combination with previously reviewed subject diary information (See Table 24), the reviewer concludes that Endometrin® use does not appear to cause serious or clinically significant local tolerability problems in the majority of subjects compared to Crinone®.

Vaginal bleeding also evaluated through daily diary cards during the first four weeks of treatment. Vaginal spotting or bleeding was experienced by 7(2%) of subjects in the Endometrin® twice daily group, 9 (2%) of subjects in the Endometrin® three times daily group and 16% (4%) in the Crinone® group. None of these subjects had severe and none had bleeding that was considered by the Investigator to have been related to the study drug. In addition, 80% of all subjects reported no genital bleeding in Study 2004-02. Table 26 outlines genital bleeding recorded on Diary Card during weeks 1 and 4 of treatment. This diary information was presented by hCG status (Week 1) and presence of fetal heart movement (Week 4):

**Appears This Way
 On Original**

Table 26: Vaginal irritation complaints reported in Study 2004-02

MedDRA term	Endometrin® 100 mg BID* (N=404)		Endometrin® 100 mg TID** (N=404)		Crinone® 8% gel QD*** (N=403)	
	N=384		N=381		N=391	
Week 1	+hCG	-hCG	+hCG	-hCG	+hCG	-hCG
None	178 (90%)	149 (80%)	203 (93%)	137 (85%)	188 (89%)	148 (82%)
Mild	16(8%)	25(13%)	12(5%)	19(12%)	21(10%)	23(13%)
Moderate	2(1%)	5(3%)	2(1%)	3(2%)	2(1%)	4(2%)
Heavy	0	7(4%)	2(1%)	1(1%)	0	4(2%)
Unknown	2(1%)	0	0	2(1%)	0	1(1%)
Week 4						
	+FHM	-FHM	+FHM	-FHM	+FHM	-FHM
None	130 (83%)	9 (82%)	134 (80%)	11 (48%)	150 (89%)	4(44%)
Mild	17(11%)	2(18%)	23(14%)	7(30%)	18(11%)	3(33%)
Moderate	5(3%)	0	6(4%)	4(17%)	1(1%)	0
Heavy	3(2%)	0	3(2%)	1(4%)	0	1(11%)
Unknown	1(1%)	0	1(1%)	0	0	1(11%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 34, page 83 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

Reviewer's comment: The reporting of events and severity of genital bleeding obtained from daily diary information appears to be clinically similar throughout the treatment groups whether or not the subject became pregnant during Study 2004-02.

7.1.6 Less Common Adverse Events

Serious vaginal irritation resulting from the concentration of adipic acid in Endometrin® was anticipated to be a less common but potentially serious adverse event. This was a concern to the Division. To evaluate vaginal irritation in more detail, an Advice letter dated July 2004 was sent to the Sponsor to perform vaginal colposcopy on all subjects in the phase 1 pharmacokinetic study (2004-01). This pharmacokinetic study would allow more intense monitoring of subjects for irritative and/or erosive damage from short-term Endometrin® use.

In Study 2004-01, the Sponsor performed a gynecologic examination and a colposcopy at screening (or prior to randomization) and at the final visit on all subjects. The Sponsor reported the following gynecologic safety data:

- No pathological colposcopic lesions or other abnormal findings were noted post-treatment, and no disruption of the surface epithelium was noted post-treatment.
- No adverse events of vaginal irritation, vaginal pain, or vaginal discharge were reported

Reviewer's comments:

1. *In Study 2005-08, gynecologic examinations were also performed in the 12 subjects who received Endometrin® for six total treatment days. These examinations were reported to be normal at screening and post-treatment in all subjects. However, the reviewer believes that the more detailed colposcopic examinations performed in 2004-01 (and the somewhat longer duration of use [10 days] are more useful in determining genital irritation/abrasion from Endometrin® than routine gynecologic examination after a very short duration of exposure.*
2. *In Study 2004-01, a review of the summaries of the gynecologic and colposcopic examinations in the 48 subjects who received Endometrin® does not indicate that any of the subjects developed a clinically significant vaginal or cervical abrasion. In this reviewer's opinion, this additional limited colposcopic information is reassuring that there is no new safety signal from vaginal administration of Endometrin® seen in close monitoring during daily administration of Endometrin®.*

In conclusion, the gynecologic information collected in the pharmacology studies (2004-01 and 2005-08) appears to support acceptable tolerability for Endometrin® use.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the 10-week Study 2004-02, laboratory tests were performed on subjects in all three treatment groups at screening and on the day of the last study visit (Week 10 or early discontinuation).

These laboratories included:

Hematology*:	white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count
Serum Chemistry*:	fasting glucose, BUN (blood urea nitrogen), creatinine, potassium, sodium, chloride, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT),
Lipid metabolism*:	Cholesterol, HDL, LDL, Triglycerides, Lipoprotein (a)
Urinalysis	
Hormone levels†:	FSH, estradiol level
Electrocardiogram:	12-lead EKG
Transvaginal ultrasound	
PAP smear†	(Only performed if not available within 12 months of screening)

*Carried out at a central laboratory

† At screening only

In Studies 2004-01 and 2005-08 (the two multiple dose pharmacokinetic studies): hematology, chemistry, lipid were conducted at screening and study completion. Urinalysis was conducted at screening and study completion in Study 2004-01. Subjects in Studies 2004-01 and 2005-08 also

had 12-Lead electrocardiograms (EKGs) were obtained at study entry and end of the treatment period). As there was no comparison placebo group, and the progesterone treatment periods were relatively short (a maximum of 10 days in Study 2004-01 and 6 days in 2005-08), no analyses of laboratory trends were performed.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. In Studies 2004-01, 2004-02 and 2005-08, no new laboratory safety signals are seen after evaluation of safety data for hematology, blood chemistry and urinalysis test results.

7.1.7.3 Standard analyses and explorations of laboratory data

Three standard approaches to the analysis of laboratory data are used where there is a suspicion of a negative impact of the drug on laboratory values. The first two analyses are based on comparative clinical trial data and the third analysis focuses on all subjects in phase 2 or 3 clinical trials. For Endometrin®, there is no comparative data from phase 2 studies in the intended subject population (patients undergoing Assisted Reproductive Technology procedures) and no comparative data that would provide information on chronic progesterone use (more than 10 days) with the progesterone insert formulation. There does not appear, however, to be any new laboratory safety signal based on the evaluation of safety data presented in Study 2004-02.

7.1.7.3.1 Analyses focused on measures of central tendency

Changes in laboratory values including hematology, chemistry and urinalysis values were assessed for changes from baseline to end of treatment were clinically evaluated for hemoglobin, platelets, ALT, AST, BUN, creatinine, and presence or absence of urine protein in Study 2004-02. Mean and standard deviations of the change from baseline to end-of study for the three treatment groups in Study 2004-02 did not demonstrate clinical differences between the treatment groups.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Clinical evaluation of outliers of clinically relevant laboratory changes that were reported as adverse events across the three treatment groups in Study 2004-02 were reviewed. None of the 1211 subjects in Study 2004-02 were considered to have a clinically significant laboratory values and no subject was discontinued because of a clinically significant laboratory adverse event.

A summary of subjects that had normal values at baseline to below normal values for hematology parameters with end-of-study abnormalities are listed in Table 27:

Table 27: Summary of key hematology laboratory abnormalities during Study 2004-02†

Hematology parameter	Endometrin® 100 mg BID N=404	Endometrin® 100 mg TID N=404	Crinone® 8% gel QD N=403
Hematocrit			
Below normal	40 (10%)	42(10%)	36(9%)
Above normal	2(<1%)	3(1%)	1(<1%)
Hemoglobin			
Below normal	18(4%)	20(5%)	21(5%)
Above normal	2(<1%)	4(1%)	26(6%)
Platelets			
Below normal	0(0%)	0(0%)	1(<1%)
Above normal	24(6%)	28(7%)	26(6%)
White blood cells			
Below normal	1(<1%)	2(<1%)	2(<1%)
Above normal	38(9%)	40(10%)	52(13%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 44, page 101 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

†This table is derived from Sponsor Table 45. The footnote to this table stated that only parameters that were normal at baseline and had at least one subject with a below or above normal value at final assessment were included in this table.

None of the shifts in the hematology laboratories list above were considered of clinical concern to the Investigators.

Reviewer's comments:

1. *The reviewer recognizes that abnormal hematology laboratories in Study 2004-02 could have had multiple etiologies, including those related to pregnancy complications, ovarian hyperstimulation syndrome and/or other preexisting medical conditions. The reviewer notes that the numbers of subjects who had hematology parameters considered outliers were clinically similar across the three treatment groups. In addition, no "panic values" were noted for hematology in any subject at their final visit.*
2. *Outliers for two hematology laboratory values were selected by the reviewer for more detailed evaluation (Platelets > 600 x10⁹/L and Anemia [defined as hemoglobin < 9 gm/dL]).*
 - a. *Platelets: Subjects with very high platelet count were evaluated as reports of purpura had been previously reported as adverse events that occurred in the original studies of luteal replacement for Crinone® (NDA 20-756). A total of 4 subjects had a platelet count > 600 x10⁹/L at the final visit (Subjects 012052, 007072, 019041 and 005097). Three of the four subjects (012052, 007072, and 019041) had high platelet counts at study initiation (defined as a value > 400 x 10⁹/L). One subjects with a platelet count > 600 x10⁹/L (005097) was in a subject using Crinone® who developed severe ovarian hyperstimulation syndrome during the study (a condition associated with increased platelets).*

Therefore, none of these laboratory outliers for platelets appear to be directly related to the study drug.

- b. Hemoglobin: Anemia was reported as an adverse event seen with in the original studies for Crinone® (NDA 20-756), and therefore very low hemoglobin values were evaluated. The reviewer noted that hemoglobin values < 9 g/dL at the final study visit (Visit 6) was not observed in any of the subjects.

In conclusion, the reviewer did not observe any other new hematology laboratory trends or safety signals for Endometrin® or Crinone® in Study 2004-02.

A summary of subjects that had normal values at baseline to below normal values for chemistry parameters with end-of-study abnormalities are listed in Table 28:

Table 28: Summary of key chemistry laboratory abnormalities during Study 2004-02†

Chemistry parameter	Endometrin® 100 mg BID N=404	Endometrin® 100 mg TID N=404	Crinone® 8% gel QD N=403
ALT			
Above normal	11(3%)	15(4%)	12(3%)
AST			
Above normal	9(2%)	9(2%)	10(2%)
Glucose			
Below normal	23(6%)	22(5%)	32(8%)
Above normal	19(5%)	11(3%)	19(5%)
Sodium			
Below normal	20(5%)	12(3%)	14(3%)
Total cholesterol			
Above normal	60(15%)	58(14%)	69(17%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 45 pages 102 of 7469.

*BID – twice daily; **TID – three times daily; ***QD – once daily

†This table is derived from Sponsor Table 45. The footnote to this table stated that only parameters that were normal at baseline and had at least one subject with a below or above normal value at final assessment were included in this table.

None of the shifts in the chemistry laboratories list reported above were considered of clinical concern to the Investigators.

Reviewer's comments:

1. The protocol for 2004-02 did not specifically define exclusion criteria for abnormal laboratory values that could be used to determine which subjects that were outliers post-treatment.

- a. The reviewer evaluated the safety dataset _____ for subjects that had a "panic value" identified by the laboratory at the end-of-study. Only one subject (07066) in the Endometrin® 100 mg three times daily group was identified as having an end-of-study "panic" value - an ALT value 256 U/L. The reviewer

b(4)

notes that this subject's mildly elevated ALT and GGT values (139 and 56 U/L, respectively) at study initiation, indicated some form of underlying hepatic abnormality prior to study initiation. In addition, the reviewer noted that Subject 025092 in the Endometrin® three times daily group also had an abnormal AST (>100) at study exit (140 U/L) as well as a high ALT (66 U/L) at the end-of-study. The etiology of these post-treatment elevations in ALT and AST is unclear, although she was reported to have mild nausea during the study, although no vomiting. However, the reviewer notes that the subject was also given oral doxycycline, propofol and fentanyl for her oocyte retrieval, which all could have contributed to nausea and elevated liver function testing.

- b. No other chemistry outlier values (including AST, total bilirubin and fasting glucose) evaluated by the reviewer raised additional concerns with Endometrin® use.*

In conclusion, the clinical reviewer does not observe any new trend or safety signal for laboratory values based on evaluation of outliers for either dose of Endometrin®.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

No subjects dropped out for laboratory abnormalities as reported in Study 2004-02 subjects. Outliers were evaluated and previously discussed in section 7.1.7.3.2 with no new safety trend or signals noted.

7.1.7.4 Additional analyses and explorations

Review of the clinical laboratory data did not provide any evidence of time-dependency, drug-demographic, drug-disease, or drug-drug interactions for Endometrin® in Study 2004-02.

7.1.7.5 Special assessments

No special assessments for hepatotoxicity or nephrotoxicity were indicated for Endometrin® inserts.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In phase 3 Study 2004-02, vital signs (systolic blood pressure, diastolic blood pressure, heart rate and temperature) were measured at baseline and at Visit 2, 3, and 6 (Also at Visits 5A and 5B if pregnant). The change from baseline was calculated for each vital sign in each the three treatment groups for each visit.

In the two phase 1 Studies (2004-01 and 2005-08), vital signs measurements were collected as part of scheduled assessments. Collection of vital sign data for each study included:

- Study 2005-08: Vital sign assessment was measured at screening, randomization prior to the re-start of study medication (beginning of the multiple-dose phase) and at the final visit.
- Study 2004-01: Vital signs were measured at screening, at Visits (prior to progesterone therapy) 2, 3, 4, and 5 (randomization), and then at Visits 6, 7, 8, 9, 10 and at the End-of-Study (Visit 11).

The Sponsor reported that for Study 2004-01 and Study 2005-08, there were no clinically meaningful differences observed at any timepoint in mean change from baseline for systolic or diastolic blood pressure or heart rate. In addition, for Study 2004-01, the Sponsor noted that all mean values for vital sign parameters remained in the normal range.

Reviewer's comment: The reviewer concurs with the Sponsor that there are no meaningful clinical differences observed during these two short-term pharmacokinetic studies that lead to the conclusion that Endometrin® use results in any meaningful clinical change in any of the measured vital signs. However, given the limited duration of exposure to Endometrin® in these two pharmacokinetic studies, conclusions on new safety trends or issues for vital signs based on the phase 1 studies (2004-01 and 2005-08) alone is insufficient for analyses. Therefore, additional analyses and exploration of vital sign data will only be performed for the phase 3 Study 2004-02.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

In the submission, only phase 3 Study 2004-02 provided a controlled comparison data that assessed the effect of the Endometrin® dosing regimens with a corresponding progesterone gel (Crinone®) dosing regimen for vital signs. In total, there were 1211 subjects in the safety population (404 in the Endometrin® twice daily group, 404 in the Endometrin® three times daily group and 403 subjects in the Crinone® once daily group).

7.1.8.3 Standard analyses and explorations of vital signs data

There were no clinically important findings based on standard analyses of vital sign data for the primary efficacy and safety Study 2004-02.

7.1.8.3.1 Analyses focused on measures of central tendencies

Central tendency analyses comparing changes from baseline to Visit 6 (Day of last dose or within 1 to 3 days) across treatment groups in the ITT group in Study 2004-02 are shown in Table 29.

Table 29: Vital Sign change from baseline to Visit 6 (or Early Discontinuation)

Change from Baseline to Last Dose	Endometrin® 100 mg BID N=404	Endometrin® 100 mg TID N=404	Crinone® 8% gel QD N=403
Systolic Blood Pressure (mmHg)	N=393	N=395	N=392
Mean change from baseline	0.1	0.12	-0.05
Standard Deviation	11.86	11.38	11.32
Minimum	-40	-36	-36
Maximum	38	46	35
Diastolic Blood Pressure (mmHg)	N=393	N=395	N=392
Mean change from baseline	-1.26	-0.9	-0.42
Standard Deviation	8.85	9.34	9.51
Minimum	-30	-28	-34
Maximum	23	29	26
Pulse Rate (bpm)	N=393	N=394	N=392
Mean change from baseline	4.66	4.86	-4.9
Standard Deviation	12.48	12.20	12.06
Minimum	-26	-28	-28.0
Maximum	46	62	68
Temperature (°F)	N=389	N=388	N=390
Mean change from baseline	-0.03	0.1	0.07
Standard Deviation	0.84	0.93	0.91
Minimum	-3.4	-4.0	-3.0
Maximum	3.3	7.6	6.0

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.3.5.1.1, pages 556, 562, 568 and 574 of 7469.

The Sponsor reported that minor mean increases and decreases in the above vital sign variables were observed in all 3 treatment groups. A statistically significant difference was observed in mean change from baseline to Visit 2 in systolic blood pressure ($p=0.019$): mean systolic blood pressure increased 2.11 mmHg in the Endometrin® twice daily group, decreased 0.30 mmHg in the Endometrin® three times daily group and increased 2.20 in the Crinone® group. The differences seen were not considered clinically meaningful by the Sponsor. No other statistically significant differences in vital sign parameters were observed in mean change from baseline to Visits 2, 3, 4, 5A, 5B or 6. The Sponsor noted that sporadic statistically significant within-group differences were observed in each treatment group. None of these differences were considered by the Sponsor to be clinically meaningful.

Reviewer's comment: The reviewer agrees that based on the vital sign data as summarized in Table 29, and the change from vital signs from baseline to the end-of-treatment, no clinical differences were observed in systolic/diastolic blood pressure, pulse rate, and temperature across the three treatment groups in Study 2004-02.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

A previous review of adverse events reported in the AERS database noted pyrexia associated with use of some progesterone products during a recent five year period. Therefore, the analyses of outliers for Endometrin® focused on changes in temperature, specifically increases in temperature. In addition, as hypersensitivity has been reported with progesterone products^{3,4}, any subject with a blood pressure reading that were considered adverse events was also evaluated separately.

Eight subjects can be considered outliers based on increased temperature (pyrexia) or abnormal blood pressure that had adverse event by the site Investigator.

- Six subjects were reported to have increased temperature as an adverse event. These subjects included:
 - Three subjects: 023022 and 003037 in the 100 mg Endometrin® twice daily treatment group
 - Three subjects: 005117, 007051, and 017052 in the 100 mg Endometrin® three times daily treatment group
 - One subject: 005006 in the Crinone® group

Two of these cases (017052 and 023022) were reported as moderate, the others were reported to be mild. None of these six febrile events were considered serious, severe or considered to have been related to the study drug by the Investigators. These two subjects were evaluated in detail and summarized. These subjects included:

- Subject 023022 in the 100 mg Endometrin® twice daily. This subject also was reported to have nausea, vomiting and post-operative pain on the same day as the increased temperature. The investigator determined that these adverse events were not related to Endometrin® use, and the adverse events above all resolved.
 - Subject 017052 in the 100 mg Endometrin® three times daily also reported chills. The investigator determined that this subjects fever and chills were not related to Endometrin® use and were reported resolved by the Investigator.
- Two subjects were reported to have blood pressure changes reported as an adverse event. These subjects included:
 - One subject: 003018 (elevated blood pressure reported as severe) in the 100 mg Endometrin® twice daily treatment group.
 - One subject 003045 (decreased blood pressure reported as moderate) in the 100 mg Endometrin® three times daily treatment group

None of these adverse events related to blood pressure were considered to have been related to the study drug by the Investigators.

Blood pressure outliers:

³Selo-Ojeme DO, Tillisi A, Welch CC. Anaphylaxis from medroxyprogesterone acetate. *Obstet Gynecol.* 2004; 103(5 Pt 2): 1045-6.

⁴Phy JL, Weiss WT, Weiler CR, Damario MA. Hypersensitivity to progesterone-in-oil after in vitro fertilization and embryo transfer. *Fertil Steril.* 2003; 80(5): 1272-5.

- Subject 003018 in the 100 mg Endometrin® twice daily treatment group (increased blood pressure). This subject also had abdominal pain, dizziness, nausea and vomiting reported on the same day as her elevated blood pressure (November 15, 2005). These adverse events were not considered by the investigator to be related to Endometrin® use and were reported as resolved by the Investigator.
- Subject 003045 in the 100 mg Endometrin® three times daily treatment group (decreased blood pressure). This subject also had gas, right lower quadrant pain, nausea, and vomiting reported on the same day as the decreased blood pressure (October 21, 2005). These adverse events were not considered related to Endometrin® use and were reported as resolved.

Reviewer's comment:

1. *The protocol for 2004-02 did not specifically define exclusion criteria for abnormal vital signs that could be used to determine which subjects were outliers. Evaluation of the outliers that were considered by the investigators to have clinically relevant vital sign changes for elevated temperature and blood pressure (reported as adverse events) does not appear to demonstrate new safety concerns with Endometrin® use.*
2. *Further evaluation of vital signs using shifts from normal to abnormal were not performed for Study 2004-02 as there were too many other confounding factors including administered medications for oocyte retrieval, oocyte retrieval and embryo transfer procedures, and pregnancy. These confounding factors prevented analysis of the effects of Endometrin® in this phase 3 patient population. However, the reviewer concludes that based on the limited adverse events for pyrexia and blood pressure (seen in this 1211 patient population of Study 2004-02 for vital sign abnormalities and the lack of these adverse events being seen in the 60 subjects treated with Endometrin® in Studies 2004-01 and 2005-08, no additional evaluation of vital signs (including assessment of shifts of vital signs) needs to be performed.*

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The protocol for Study 2004-02 did not pre-specify what a marked outlier for temperature and blood pressure was. Only one subject was reported to have been discontinued for a vital sign abnormality (elevated temperature):

- Subject (003037) was discontinued from Study 2004-02 for elevated temperature prior to her embryo transfer. This subject was randomized after oocyte retrieval to the Endometrin® twice daily treatment group (October 8, 2005). On October 10, 2005, the subject returned with a postnasal drip, cough, and elevated temperature. The subject was determined to have a mildly elevated temperature (101.5°F). The investigator determined that she should not have an embryo transfer with an elevated temperature, and discontinued this subject from the study. The reviewer agrees that the cause of the elevated temperature was not related to the study drug.

Reviewer's comments:

1. *The reviewer evaluated the Sponsor's dataset (VS) for marked outlier analysis for temperature and blood pressure. The reviewer evaluated the safety dataset for subjects with:
 - *Temperature $\geq 101^{\circ}\text{F}$*
 - *Diastolic blood pressure ≥ 110 mmHg**
2. *The reviewer determined that no subjects had temperatures $\geq 101^{\circ}\text{F}$ other than Subject 003037 as outlined above.*
3. *The reviewer noted that there was only one subject with diastolic blood pressures ≥ 110 mm Hg at a post-screening visit that was in the Endometrin® twice daily treatment group. This subject (026044) had a diastolic blood pressure of at Visit 3. This subject was taking diazide and toprol for her hypertension prior to initiation of the study, and had a blood pressure at screening of 130/82. Her blood pressure reading increased to 156/110 at Visit 3, but decreased by Visit 6 to 132/89. This blood pressure reading was not considered an adverse event by the site Investigator and based on her history of requiring chronic treatment for hypertension, the reviewer agrees that this elevated blood pressure was not related to her Endometrin® use.*

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In both phase I Studies (2004-01 and 2005-08); 12-lead electrocardiograms were collected on all subjects at screening and at the end of study (or discontinuation) after completing 6 to 10 total days of progesterone treatment. The Sponsor reported that:

- Study 2004-01: None of the 48 subjects treated with Endometrin® were reported to have a clinically meaningful change in ECG from baseline, and all mean values for ECG parameters remained within the normal range.
- Study 2005-08: All 18 subjects treated with Endometrin® or Crinone® had normal ECGs at baseline and at the post-treatment visit.
- Study 2004-02: A total of two subjects of 1211 had reports of cardiac arrhythmias. These subjects included: Subject 005037 who was reported to have tachycardia of moderate severity, and Subject 019127 who was reported to have had an irregular heartbeat of mild severity. The investigators at the sites where these subjects were seen determined that both of these cardiac adverse events resolved, (although the tachycardia required treatment). Neither of these cardiac events were determined by the site investigator to have been related to the study drug.

In active-controlled phase 3 Study 2004-02, no electrocardiograms were performed.

Reviewer's comments:

1. *The reviewer evaluated the QT_C interval and other abnormalities from the dataset EG.XPT provided by the Sponsor for the two phase 1 studies. The reviewer agrees with the Sponsor that none of the 48 subjects treated with Endometrin® in Study 2004-01 had any clinically significant findings.*
2. *The reviewer agrees that the few EKG abnormalities that were noted in 2004-01 and 2004-02 do not appear to be clinically significant. In conclusion, the reviewer does not see any new safety trends for EKG abnormalities with use of progesterone inserts based on the limited data presented from the 60 subjects*
3. *Studies 2004-01 and 2005-08 did not control when the ECGs were performed relative to drug concentrations. In addition, these two pharmacokinetic studies were not placebo-controlled and were very short in duration of progesterone treatment (maximum treatment of 6-10 days with progesterone). Therefore, these two studies will not be reviewed further regarding EKG changes.*

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made given the limited ECG data available.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

No other standard analyses and explorations of ECG testing were performed for Studies 2004-01, 2004-02 or 2005-08.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

No other standard analyses and explorations of ECG testing were performed for Studies 2004-01, 2004-02 or 2005-08.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No other standard analyses of marked outliers or dropouts from ECG testing were performed for Studies 2004-01, 2004-02 or 2005-08.

7.1.9.4 Additional analyses and explorations

No separate QT/QTc prolongation study or additional analyses of ECG data were performed for Endometrin®. As noted in Section 7.1.9.1, no ECG data were obtained from subjects in the primary phase 3 Study 2004-02 and no ECG information was provided for Study 2005-08.

Reviewer's comment: The Clinical and Clinical Pharmacology reviewers agree that based on the current available safety information on progesterone for use in luteal supplementation and replacement, more detailed EKG studies are not necessary.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted with the NDA regarding immunogenicity of Endometrin®.

7.1.11 Human Carcinogenicity

No nonclinical or clinical carcinogenicity studies were conducted for Endometrin®.

Reviewer's comment: In this reviewer's opinion, class labeling for progesterone-containing products for the human carcinogenicity section is acceptable. The current labeling for other progesterone products will be recommended for the Endometrin® label, "Nonclinical toxicity studies to determine the potential of Endometrin® to cause carcinogenicity or mutagenicity have not been performed. The effect of Endometrin® on fertility has not been evaluated in animals."

7.1.12 Special Safety Studies

The following special nonclinical safety studies were performed for toxicology evaluation and reviewed by the Pharmacology/Toxicology reviewer for Endometrin®:

- A 14-day vaginal irritation/toxicity study in rabbits
- A 90-day vaginal irritation/toxicity study in rabbits
- A primary irritation study in rabbits
- A dermal sensitization study in guinea pigs

For more information on these studies, please see the Pharmacology/Toxicology review of NDA 22-057/S-000 dated May 14, 2007.

No additional non-clinical or additional clinical safety studies were recommended for Endometrin® inserts (NDA 22-057).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Per the submission, no statement on abuse potential is considered necessary in the labeling for Endometrin® and the Sponsor states that "The half-life of progesterone is _____ and Endometrin® is expected to have a half-life of _____ (Ferring Study 2005-08); any effects of Endometrin® would be expected to clear from the body quickly." The potential for over dosage with progesterone supplementation is not expected to be different than for other approved progesterone products. Based on the results of clinical Study 2004-02, the Sponsor has proposed the following language for the OVERDOSAGE section of the label:

b(4)

b(4)

Reviewer's comment: The language in the OVERDOSAGE section of the label as proposed by the Sponsor is acceptable, given the results in clinical Study 2004-02.

7.1.14 Human Reproduction and Pregnancy Data

Successful clinical pregnancies require progesterone for luteal support from the ovary for the first weeks until the fetal placenta is able to manufacture adequate progesterone levels. The use of exogenous progesterone to support the luteal phase for women undergoing ovarian stimulation for Assisted Reproductive is considered necessary. It is felt that without exogenous progesterone supplementation, pregnancy in these women will be unlikely to occur.

The dosage, administration and timing of progesterone use in various ART protocols are somewhat variable across different ART sites in the US. Many clinical protocols include use of intramuscular injections of progesterone in oil, (although the use of this progesterone product is off-label). The reason for this continued off-label use of progesterone in oil dates back to the initial ART studies. These studies used progesterone in oil as one of the first progesterone products used for luteal support after ART procedures that achieved a successful pregnancy.

To date, there is only limited pregnancy outcome data for progesterone use as luteal support after Assisted Reproductive Technology (ART) procedures. The majority of the information on pregnancy outcomes with luteal support is obtained from 1) Published literature on ART, and 2) postmarketing information for the currently approved progesterone products in the US. This pregnancy outcome information has not raised safety concerns about any progesterone product on pregnancy, fetal development or congenital malformations in the first trimester after Assisted Reproductive Technology therapy.

Study 2004-02 provided follow-up pregnancy outcome data for Endometrin® and Crinone® after the period of luteal support was completed. The pregnancy outcome information supplied included: 1) livebirth rates 2) multiple pregnancy rates and 3) pregnancy loss rates by treatment group. The livebirth rates per retrieval for the ITT population by treatment assignment included:

- Endometrin® twice daily = 141 of 404 subjects (35%)
- Endometrin® three times daily = 154 of 404 subjects (38%)
- Crinone® once daily = 153 of 403 subjects (38%)

Reviewer's comment: The overall livebirth rates did not appear to be clinically or statistically different (95% lower bound of the confidence interval for Endometrin® twice daily and three times daily was -9.7 and -6.5, respectively).

In addition, it is reassuring that the livebirth rates seen with the two Endometrin® treatment arms slightly exceeded the reported 2002 livebirths per retrieval was at a rate of 31.6% (in the general ART population in 2004).⁵

The multiple pregnancy rates for the ITT population by treatment assignment are seen in Table 30. No multiple pregnancies were conceived with more than triplets in any of the three treatment groups. For the overall ITT population, 14 to 18% of subjects conceived twins, and 2% conceived triplets. Multiple pregnancy rates were also evaluated using subgroups by age, ovarian reserve, type of insemination, use of assisted hatching or day of embryo transfer. The Sponsor reported the multiple pregnancy rates were similar across the groups (including rates for singletons, twins or triplets).

Table 30: Rates of subjects with multiple pregnancies (on ultrasound) stratified by ART methodology

ITT population	Endometrin® 100 mg twice daily	Endometrin® 100 mg three times daily	Crinone® 8% gel once daily
Subjects with ongoing pregnancy	156	171	170
Multiple pregnancies			
Twins	62	70	57
Triplets	6	4	7
Total subjects by type of insemination			
ICSI	287	278	299
IVF	116	123	99
Multiple pregnancies -ICSI (n)	48	53	51
Multiple pregnancies - IVF (n)	24	25	15
Subjects by Day of embryo transfer			
Day 3	241	236	225
Day 5	127	126	133
Multiple pregnancies -Day 3 (n)	42	46	26
Multiple pregnancies - Day 5 (n)	28	29	38

Source: Adapted from NDA 22-057/S-000, Safety Update for Study 2004-02 dated 22-Dec-06, Attachment 16 – Cross references Tables 14.3.5.7.2, 14.3.5.7.3, 14.3.5.7.4 and 14.3.5.7.5, page 7 of 14.

Reviewer's comments:

- *The overall subjects who had multiple pregnancies across the treatment groups appear somewhat higher overall in the Endometrin® arms compared to the Crinone®, but are not increased over what is might be expected as a result of ART procedures.*

⁵Center for Disease Control and Prevention. 2004 Assisted Technology Success Rates. December 2006.

- *The subjects with multiple pregnancies were higher in the Endometrin® treatment arms for Day 3 transfers, and in those with IVF compared to Crinone®, while being lower in those with Day 5 transfer and equivalent for ICSI to the Crinone® treatment group. These multiple pregnancy rates cannot be compared to national rates as the national rates are per cycle, not per transfer. In fact, after review of the published literature, this reviewer concludes that the etiology of multiple pregnancies is directly related to the number of embryos transferred, and culture conditions rather than related to Endometrin or progesterone use.*

In conclusion, it is unclear why subjects in the Endometrin® treatment groups have higher multiple pregnancy rates when compared to the Crinone® group. It is possible that the lack of randomization between days 3 and 5 transfer (as day 5 is less likely to produce multiple pregnancies) may be a possible explanation.

A subgroup analysis of actual rates of singletons compared to twins and triplets was performed to evaluate the multiple pregnancy data. These results are seen in Table 31:

Table 31: Multiple Pregnancies (seen on ultrasound) by Treatment Group by Number of Sacs

ITT population	Endometrin® 100 mg twice daily	Endometrin® 100 mg three times daily	Crinone® 8% gel once daily
Total multiple pregnancies	N=236	N=255	N = 244
Singletons n (%*)	88 (37%)	97 (38%)	106 (43%)
Twins n (%*)	124 (53%)	140 (55%)	114 (47%)
Triplets n (%*)	18 (8%)	12 (5%)	21 (9%)

*Total number of pregnancies

Source: Adapted from NDA 22-057/S-000, Safety Update for Study 2004-02 dated 22-Dec-06, Attachment 16 - Tables 14.3.5.7.1 and 14.3.5.7.6 and 14.3.5.7.7 pages 9 of 14 and an addendum dated March 1, 2007.

Reviewer's comment: The numbers in this table include all multiple pregnancies seen on ultrasound. Although there were a few more twin pregnancies in the Endometrin® treatment groups compared to Crinone® group, the triplet numbers were roughly equivalent. No multiples above triplets were reported in any treatment arm. This reviewer notes that the most likely etiology of these multiples is the number of embryos transferred, not the effect of progesterone. However, it is reassuring to this reviewer that the multiple pregnancy numbers appear to be clinically similar between the treatment groups.

The abnormal pregnancy outcome data for the ITT population was summarized by treatment assignment and are seen in Table 32.

Table 32: Post-Study 2004-02 Pregnancy Follow-up (% per retrieval)

Pregnancy Outcome	Endometrin® 100 mg twice daily N = 404	Endometrin® 100 mg three times daily N = 404	Crinone® 8% gel once daily N = 403
Selective reduction	4(1%)	2(0.5%)	5(1.2%)
Miscarriage following chorionic villus sampling	0	1 (0.2%)	0
Spontaneous abortion	13 (3.2%)	22 (5.4%)	13 (3.2%)
Ectopic pregnancy†	1 (0.2%)	4(1.0%)	3 (0.7%)
Elective Abortion	2 (0.5%)	5(1.2%)	3 (0.7%)
2 nd trimester fetal loss	8 (2.0%)	2 (0.5%)	7 (1.7%)
3 rd trimester fetal loss	1 (0.2%)	0	0
Fetal anomalies	3 (0.7%)	5 (1.2%)	1 (0.2%)
Still birth	1 (0.2%)	1 (0.2%)	2 (0.5%)

Source: Adapted from NDA 22-057/S-000, Safety Update for Study 2004-02 dated 22-Dec-06, Table 14.3.5.9, page 1 of 1.

†Ectopic pregnancy rates from NDA 22-057, Final Study Report Table 14.2.8.1 page 248 of 7469.

Reviewer's comment: The fetal loss rates for all categories, when totaled, appear to be clinical similar across the treatment groups. In addition, these rates of fetal loss are lower than the observed rate in the general population of ART patients which is approximately 15% (2004 ART statistics).⁶

A subgroup analysis of actual rates of livebirth singletons compared to twins and triplets was performed to further evaluate the multiple pregnancy data. These results are seen in Table 33:

Table 33: Post-Study 2004-02 Livebirths separated by number of babies delivered

ITT population	Endometrin® 100 mg twice daily	Endometrin® 100 mg three times daily	Crinone® 8% gel once daily
Singletons n	85	91	97
Twins n	56	60	54
Triplets n	2	4	4

Source: Adapted from NDA 22-057/S-000, Safety Update for Study 2004-02 dated 22-Dec-06, Table 14.3.5.9, page 1 of 1 and an Amendment dated March 1, 2007.

A post-study collection of birth information was collected by the Sponsor. A total of 16 children of 643 livebirths were born with birth defects (4%). In the individual treatment arms, the following fetal birth defect rates were noted:

- Endometrin® twice daily = 7 of 203 livebirths (3.4%)
- Endometrin® three times daily = 7 of 223 livebirths (3.1%)

⁶ Center for Disease Control and Prevention. 2004 Assisted Technology Success Rates. December 2006.

➤ Crinone® once daily = 2 of 217 livebirths (0.9%)

A more detailed overview of the reported birth defects seen in Study 2004-02 is listed below in Table 34:

Table 34: Birth defects reported in Study 2004-02

Treatment Group	Description of Fetal Anomaly
Endometrin® 100 mg twice daily	1. Cleft palate/intrauterine growth retardation 2. Spina bifida/myelomeningocele 3. Aortic stenosis 4. Umbilical hernia 5. Intestinal abnormality 6. Translocation of heart valves 7. Congenital heart defect
Endometrin® 100 mg three times daily	1. Esophageal fistula 2. Underdeveloped right ear/hypospadias 3. ASD/Down's* 4. Small aorta/inadequate heart valve closure/deviated heart septum 5. DiGeorge's syndrome 6. Hand deformity 7. Cleft palate
Crinone® 8% gel once daily	1. Ankyloglossia 2. Esophageal atresia

Source: Adapted from NDA 22-057/S-000, Safety Update for Study 2004-02 dated 22-Dec-06, Listing 16.2.6.5, page 156 of 193 and from an Amendment dated March 1, 2007.

Reviewer's comments:

1. *After initial evaluation, it would appear that the two treatment arms of Endometrin have a higher rate of birth defects when compared to single Crinone® treatment arm. This reviewer believes that although the number of birth defects is numerically higher in the two Endometrin arms, these birth defect findings are not clinically concerning or significant. The reasons for this reviewer's conclusions are based on the following information:*
 - a. *The FDA Guidance Document Entitled, "Evaluating the Risks of Drug Exposure in Human Pregnancies (dated April 2005) report that about 4% of babies born in the United States (general population) have a major birth defect or congenital malformation (the source quoted in the guidance document is the March of Dimes (2001). The rates seen for the two Endometrin arms are clinically similar to this quoted general population rate in the guidance.*
 - b. *The reported rate of birth defects on the CDC website (2007) for the general population is 3%.⁷ The reported CDC rate is also clinically similar to those seen in each of the two Endometrin® treatment arms.*

⁷ <http://www.cdc.gov/ncbddd/bd/faq1.htm#CommonBD>.

This reviewer recognized that any definitive conclusions on the birth defects are limited as Study 2004-02 was not powered to look at the rate of birth defects. However, the birth defect information appears to show acceptable safety evidence that Endometrin® does not contribute to an increased rate of birth defects by itself. However, the Clinical review team will continue to monitor for birth defects post-marketing.

Neither of the pharmacokinetic studies (2004-01 and 2005-08) provided any additional information on Endometrin® drug exposure or birth defects in pregnant women.

7.1.15 Assessment of Effect on Growth

In the US, progesterone drug product class labeling states that the safety and efficacy of progesterone drug products has not been established in pediatric or adolescent patients.

7.1.16 Overdose Experience

There are no reports of overdosage of Endometrin® in the primary efficacy and safety Study 2004-02. In addition, there are no published reports of overdosage from vaginal or orally administered progesterone products that can be used to make any specific clinical recommendations.

7.1.17 Postmarketing Experience

One other vaginal product containing progesterone (Crinone® [NDA 20-756]) is marketed both internationally and in the United States for luteal replacement or luteal supplementation after Assisted Reproductive Technology procedures. The AERS post-marketing database for Crinone® does not reveal any new safety concerns for use of this product for luteal supplementation that were not evaluated in Study 2004-02.

The Sponsor reported that the first marketing authorization for Endometrin® (0.5 mg and 1.0 mg doses) was approved in Israel and Hong Kong since 2003. Endometrin sales figures for Israel were — inserts in 2005 and — inserts in 2006. In Hong Kong, Endometrin sales figures were — inserts in 2005 and — inserts in 2006. The Sponsor reported that there were several previous publications that exposed a combined total of 683 women to Endometrin® after various Assisted Technology procedures. In 2004, the Sponsor reported that product tolerability was assessed by questionnaires to Israeli centers that prescribed Endometrin® for luteal support after Assisted Reproductive Technology procedures. At that time, the Sponsor estimated that approximately 3,500 patients had been treated in over 6,000 clinical cycles at those centers with an ongoing pregnancy rate of approximately 25%.

b(4)

The Sponsor also notes that since being marketed in Israel and Hong Kong, only one post-marketing adverse event has been reported to Ferring (November 2004). This report detailed a patient who was on a combination of Estrofem®, Endometrin® and Gestone® for luteal support who developed severe abdominal and pelvic pain radiating to the left leg and subsequently was hospitalized and found to have an ongoing normal singleton pregnancy. The pain apparently

subsided after discontinuing luteal support without a clear diagnosis, but it is unclear from this report whether a single drug product or combination caused this pain.

Reviewer's comment: The reviewer notes that the timing between embryo transfer and the pain is unclear and the transfer procedure could have contributed to the pain. With the limited information in this report, the reviewer agrees with the Sponsor that this event was unlikely to have been caused by the Endometrin®

In the most recent periodic safety update (dated December 22, 2006), the Sponsor reported there were no outstanding regulatory actions regarding Endometrin® in Israel and Hong Kong. The Sponsor also reported that an additional spontaneous adverse event was reported for Endometrin® since the time of the initial NDA submission in August 2006. This patient was switched from an oral progesterone formulation to Endometrin® at 7 weeks gestation (The rationale for the switch is unclear). The patient developed vomiting, dizziness, palpitations and chest pain after receiving her first dose of Endometrin®. Endometrin® was discontinued and the adverse events abated. This event was classified by the reporter (a physician) as possibly related to Endometrin®.

Reviewer's comment: The reviewer agrees with the Sponsor that it is difficult to determine the actual etiology of this patient's adverse events, although it is plausible that she had an allergic or anaphylactoid reaction to Endometrin®. This post-marketing report appears to emphasize the need for the Sponsor to monitor for reports of allergic or anaphylactic reactions from Endometrin®.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical studies submitted with NDA 22-057/S-000 (as outlined in Section 4.2) summarize all clinical studies submitted to support the safety and efficacy of the 100 mg progesterone vaginal insert. Only Study 2004-02 was used for evaluation of efficacy, although the two pharmacokinetic studies (2004-01 and 2005-08) collected limited safety data. There was adequate representation for infertile women undergoing Assisted Reproductive Technology procedures in Study 2004-02.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for summaries of study design and number of subjects in each study.

7.2.1.2 Demographics

The demographics and baseline characteristics of Study 2004-02 for m-ITT cohort by treatment group are summarized in Table 35. Overall, there were no major differences seen across groups:

ages ranged from 19 to 42 years with a mean of 33 years in all treatment groups. Sixty to 61% of subjects in each treatment group were younger than 35 years of age and approximately half of the subjects in each group had a body mass index (BMI) of between 18.5 and 24.9 kg/m² in each group.

Table 35: Subject Demographics and Baseline Characteristics (m-ITT Cohort)

Characteristic		Endometrin® 100mg BID N=404	Endometrin® 100mg TID N=404	Crinone® 8% gel QD N=403
Race	N	404(100%)	404(100%)	404(100%)
	Caucasian	304(75%)	299(74%)	306(76%)
	Black	20(5%)	24(6%)	30(7%)
	Asian	20(5%)	21(5%)	20(5%)
	Hispanic	40(10%)	43(11%)	34(8%)
	Other	20(5%)	17(4%)	13(3%)
Age (years)	Mean	33.1	33.0	33.1
	SD*	4.30	4.40	4.34
Weight (lbs)	N	(N=402)	(N=404)	(N=402)
	Mean	148.0	148.6	148.5
	SD*	27.21	27.35	28.76
BMI (kg/m ²)	N	(N=402)	(N=404)	(N=402)
	Mean	24.9	25.0	24.9
	SD*	4.10	4.22	4.14
Systolic BP (mmHg)	N	(N=402)	(N=404)	(N=401)
	Mean	112.6	113.2	112.9
	SD*	11.21	11.22	11.12
Diastolic BP (mmHg)	N	(N=402)	(N=404)	(N=401)
	Mean	72.5	73.0	71.9
	SD*	8.77	9.31	9.04
Heart Rate (bpm)	N	(N=402)	(N=404)	(N=401)
	Mean	72.9	73.0	71.9
	SD*	9.22	9.31	9.04

*SD – Standard deviation

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Tables 14.1.2.1, 14.1.2.1, and 14.1.5, pages 153, 154 and 167 of 7469.

Reviewer's comment: No clinically significant differences in demographics as summarized in Table 35 are observed between the three treatment groups.

Infertility diagnosis were similar across the 3 treatment groups in the ITT population, with approximately one-third of subjects each had male factor or tubal factor as the etiology of infertility. Infertility diagnoses of all subjects are summarized in Table 36:

Table 36: Infertility diagnosis – ITT population

Infertility Diagnosis	Endometrin® 100 mg BID* (N=404)	Endometrin® 100 mg TID* (N=404)	Crinone® 8% gel QD* (N=403)
Male factor (yes)	139 (34%)	147 (36%)	144(36%)
Tubal factor (yes)	117 (29%)	138 (34%)	132 (33%)
Endometriosis (yes)	94 (23%)	76 (19%)	100 (25%)
Ovulatory dysfunction (yes)	81 (20%)	85 (21%)	80 (20%)
Uterine factor (yes)	10 (2%)	13 (3%)	16 (4%)
Unexplained infertility	83 (21%)	91 (23%)	90 (22%)
Other	34 (8%)	32 (8%)	33 (8%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.1.3, page 161 of 7469.

Reviewer's comment: The reviewer agrees with the Sponsor that no clinically significant differences in infertility diagnoses were seen. In addition, no clinically significant difference in the three treatment groups demographics in terms of previous obstetric histories was noted. There were no clinical differences in the numbers of previous full term births (mean of 0.4 across the three treatment groups), previous abortions (mean of 0.5 across the three treatment groups) or previous ectopic pregnancies (mean of 0.2 by history across the two Endometrin® treatment groups and the Crinone® treatment groups.

7.2.1.3 Extent of exposure (dose/duration)

Twelve hundred eleven (1211) subjects were randomized to receive one of the three treatment groups in primary, phase 3 Study 2004-02 and received study drug or comparator. The overall days of exposure to study medication were comparable across the three treatment groups for the 1211 subjects in the safety cohort (see Table 37).

Table 37: Extent of Exposure in Days (Safety Cohort)

Time (Days)	Endometrin® 100 mg twice daily N=404	Endometrin® 100 mg three times daily N=404	Crinone® 8% vaginal gel N=403	Total (N=1211)
Mean	80.9	82.1	82.5	81.6
Std	19.85	16.90	15.26	17.41
Minimum	3	1	8	1
Maximum	111	109	100	111
Median	85.0	85.0	85.0	85.0

Source: Adapted from NDA 22-057/S -000, Final Report for Study 2004-02, Table 12.1-1, page 96 of 7469.

Reviewer's comment: The days of exposure to progesterone appear to be clinically similar between the three treatment groups. The limited number of pharmacokinetic samples in the phase 3 study, and the confounding effects of hCG injection, endogenous progesterone production from the ovary (and after 7 weeks from the placenta if the subject is pregnant) and

significant intra-subject variations in progesterone, make comparisons of PK from the three treatment groups in Study 2004-02 inconclusive to make predictions about extent of exposure resulting from exogenous progesterone.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were submitted

7.2.2.2 Postmarketing experience

Endometrin® has been marketed in Hong Kong and Israel since 2003. Sales in Israel were reported to be: — inserts in 2005 and — inserts in 2006. Sales in Hong Kong were — inserts in 2005 and — inserts in 2006. Only one postmarketing adverse event has been reported to the Sponsor since approval in Hong Kong and Israel since 2003 (described previously in section 7.1.12)

b(4)

There is US postmarketing experience with another approved vaginal progesterone product (Crinone® 8% vaginal gel, now marketed under the name Prochieve®). This progesterone vaginal gel is also indicated for luteal supplementation in patients undergoing Assisted Reproductive Technology procedures. Postmarketing data has been collected since approval of the progesterone vaginal gel in 1997. Of note, this progesterone vaginal gel also is indicated for treatment of secondary amenorrhea in women. This postmarketing data in the United States for the progesterone vaginal gel is available through the FDA's Adverse Events Reporting System (AERS) and annual reports for this product. No safety signals have arisen from review of these adverse events to date.

7.2.2.3 Literature

The Sponsor provided a current reference list of two meta-analysis of publications of progesterone use for luteal supplementation, a recent review of the available literature on luteal support and recent pregnancy outcome information for subjects having donor and assisted reproductive technology therapies. In addition, the Sponsor provided three additional publications on the pharmacokinetics and pharmacodynamics of progesterone use in women. These publications adequately document potential risks and benefits of progesterone use for supplementation in patients undergoing Assisted Reproductive Technology (ART) therapy. No additional clinical safety concerns for luteal supplementation with progesterone use were noted in the provided published literature.

7.2.3 Adequacy of Overall Clinical Experience

A total of 808 healthy infertile subjects who were undergoing Assisted Reproductive Technology procedures were exposed to vaginal administration of 100 mg Endometrin® inserts in Study

2004-02 (404 subjects to the twice daily regimen, and 404 subjects to the three times daily regimen).

A total of 60 subjects were exposed to progesterone inserts administered vaginally in Studies 2004-01 and 2005-08 (the multiple dose pharmacokinetic studies). Pharmacokinetic parameters were evaluated in:

- Study 2004-01: 48 subjects were randomized to one of three dosage strengths (50 mg, 100 mg and 200 mg) and two administration regimes (once daily or twice daily) of Endometrin® applied vaginally for 10 days.
- In Study 2005-08, 12 subjects were randomized two on of two dosage regimes (100 mg twice daily or 100 mg three times daily) for a total of 6 treatment days.

Only Study 2004-02 was of 10 weeks duration and in the target population of subjects undergoing Assisted Reproductive Technology procedures. The multiple dose pharmacokinetic studies (2004-01 and 2005-08) were not placebo-controlled, and were in healthy premenopausal women.

As recommended by the ICH guidance on extent and duration of exposure, long-term safety data should be collected on a sufficient number of subjects for a sufficient duration to assess safety for chronic use drugs. Progesterone drug products for luteal supplementation are not intended for chronic use. Labeling will recommend the 10-week treatment regimen evaluated in Study 2004-02.

Study 2004-02 provided both efficacy and safety data. The inclusion and exclusion criteria for participants in Study 2004-02 were appropriate. Inadequate representation of race was represented in Study 2004-02, however, since 75.1% of participants were Caucasian.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Use of progesterone in clinical practice began in the 1930s with the extraction and purification of progesterone. Therefore, the only four additional nonclinical studies for Endometrin® requested were to evaluate vaginal irritation, dermal sensitization study, skin irritation study and a 3-month repeat dose vaginal toxicity study that supported clinical exposure in women for the clinical study that would treat subjects for 10 to 12 weeks in duration.

These four additional nonclinical studies were reviewed by the Pharmacology Toxicology reviewer. Endometrin® was rated in dermal studies to be a non-sensitizer and not a vaginal irritant. After review of the four additional submitted nonclinical studies, the Pharmacology/Toxicology reviewer concluded that no new toxicity was seen. For more information please see the Pharmacology/Toxicology review for NDA 22-057/S-000 dated May 14, 2007.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of Study 2004-02 subjects presented in this submission, including efforts to monitor laboratory parameters, vital signs, and efforts to elicit adverse event data is adequate. Hematologic, chemistry, lipid and liver laboratory parameters, were collected at baseline and end of study (Treatment week 10 or early discontinuation) and subjects were compared to their baseline values in the primary phase 3 Study 2004-02.

The same comparison of laboratory values was performed in the multiple dose pharmacokinetic studies (Studies 2004-01 and 2005-08).

Key laboratory parameters collected were evaluated using standard limits and values from a central laboratory [redacted]. The routine laboratory evaluations and procedures performed appear to have been adequately assessed by qualified personnel.

b(4)

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review gives a brief summary of the clinical pharmacology for Endometrin® inserts (See the Clinical Pharmacology and Pharmacokinetics Review dated May 24, 2007 for a more complete discussion). The metabolism and excretion of progesterone drug products are sufficiently understood as use dates back to the 1930s to ease concerns about safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

No other pharmacokinetic data on metabolism, clearance or drug interaction of progesterone products over the period of the 10 to 12 week treatment duration was submitted by the Sponsor. Submission of additional pharmacology data was not requested in accordance with the Federal Register Notice dated 09 Sep 1971 on requirements for submission for progesterone drug products.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The current adverse event database for Endometrin® was comprised of the phase 3 clinical Study 2004-02, and adverse event reporting from the two pharmacokinetic phase 1 studies (Studies 2004-01 and 2005-08). The available adverse event information from these three clinical studies in over 800 subjects who used Endometrin® is sufficient for approval.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data submitted in NDA 22-057/S-000 for the safety cohort of 1211 randomized subjects was adequate to assess adverse events that might be expected for progesterone class drug products.

7.2.9 Additional Submissions, Including Safety Update

A safety update was submitted to NDA 22-057 (electronic submission date 22-Dec-06) that provided additional safety information on Endometrin® marketing experience outside the United States. In this timeframe since the original submission in August 2006, the following was reported:

1. There were no outstanding regulatory actions in the two countries where Endometrin® is currently marketed (Israel and Hong Kong).
2. One new adverse event was submitted in the safety update as occurring since the initial NDA submission in August 2006. This spontaneous adverse event report was a 32 year old woman who was 7-weeks pregnant and switched from Utrogestan® (progesterone capsules administered orally [tradename Prometrium® in the United States]) to Endometrin®. The subject reported that after the first dose of Endometrin® she experienced vomiting, dizziness, chest pain and palpitations. Endometrin® was discontinued and the symptoms resolved. The reported determined the relationship between the drug and the adverse event to be possible.
3. An additional publication on the local tolerability of Endometrin® was also submitted (Ng, et al, 2006) with the safety update. This study described side effects and vaginal tolerance of Endometrin® compared to Cyclogest® (vaginal progesterone suppositories – not approved in this country) in 132 subjects undergoing Assisted Reproductive Technology procedures at one center.¹³ In this study, 67 subjects received Endometrin® and 65 received Cyclogest® for luteal support. The primary outcome for this study was perineal irritation. In this study:
 - 6 (9.1%) complained of perineal irritation in the Endometrin® group on treatment day 6 (compared to 8 subjects – [12.1%] in the Cyclogest® group)
 - 5(7.6%) complained of perineal irritation in the Endometrin® group on treatment day 16 (compared to 10 subjects – [15.2%] in the Cyclogest® group)
 - Other side effects reported (but not by treatment group or percentage) including nausea, vomiting, constipation, diarrhea, stomach pain, headache, breast fullness, joint pain, irritability, drowsiness, inhibited sexual desire, dyspareunia, and nocturia. The authors did report that these side effects were comparable between the two groups at treatment days 6 and 16.

Reviewer's comments:

1. *No new safety issues for Endometrin® were seen after review information from the most recent study by Ng, et al and the single post-marketing case report submitted.*
2. *The Sponsor reported that no additional clinical studies have been conducted by the Sponsor (Ferring) with Endometrin® since submitting the application for review.*

**Appears This Way
On Original**

¹³Ng E, Chan C, Tang O, Ho C. A randomized comparison of side effects and patient convenience between Cyclogest® suppositories and Endometrin® tablets used for luteal phase support in IVF treatment. Eur J Obstet Gynecol Reprod Biol 2006 Aug 17 [Epub ahead of publication].

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

All progesterone-containing drugs primarily impact the reproductive and breast organ systems. Therefore, of the adverse events seen with Endometrin® treatment in the primary efficacy and safety Study 2004-02, the most concerning drug-related events are those observed in the reproductive system and breast disorders group. In this reproductive and breast disorder AE group, a total of 220 AEs were reported, and the occurrence of AEs did not appear to be dose proportional, but roughly equivalent across the treatment groups. Specifically, a total of 69 reproductive and breast adverse events were seen in the Endometrin® twice daily group, 74 events in the Endometrin® 100 mg three times daily group compared to 77 events in the Crinone® one daily group. The most frequently reported reproductive system and breast disorders AE was ovarian hyperstimulation syndrome (OHSS). OHSS was reported in 6.9% of total patients (7.4%, 6.7% and 6.5% for the Endometrin® twice daily group, the Endometrin® three times daily group and the Crinone® treatment group, respectively). None of the reproductive adverse events reported appear to represent a new safety signal or safety trend for Endometrin®.

Reviewer's comment: In fact, this reviewer notes that the observed rates of ovarian hyperstimulation seen in the treatment groups for Study 2004-02 are clinically similar to those seen in a previous gonadotropin studies (Overall 6.8% in Study 2004-02 compared to 7.2% of subjects seen in another recent gonadotropin study [See the Medical Officer's Review of NDA 21-663 – Study MFK/IVF/0399E for Menopur® dated October 29, 2004].

Progesterone provides some protection of the endometrium for patients who have secondary amenorrhea and those using estrogen-containing products from hyperplasia and cancer. Of note the primary efficacy and safety study (Study 2004-02), provided no supportive histologic information on the endometrial safety for Endometrin®. However, Study 2004-01 provided some 47 endometrial histologic reports after 10 days of use in healthy pre-menopausal women. Review of this endometrial histology and concomitant ultrasound findings in Study 2004-01 did not demonstrate new safety signals or trends for Endometrin®. However, this limited histology provided is sufficient to provide supportive evidence for the short-term (10 weeks) duration of treatment proposed for Endometrin® in women after Assisted Reproductive Technology procedures.

Endometrial safety for progesterone-only products also is evaluated by the overall rate of vaginal bleeding. These adverse events (which were coded as either Vaginal Haemorrhage or Metrorrhagia) were reported in 4.0% of the total safety population in Study 2004-02 (3.2%, 3.5%, and 5.5% patients for the Endometrin® 100 mg twice daily, Endometrin® three times daily and Crinone® treatment groups, respectively). None of these vaginal bleeding adverse events were reported as severe or serious, and no subjects discontinued for vaginal bleeding. The reviewer notes that in Study 2004-02, subjects had a number of other reasons for vaginal bleeding, including abnormal pregnancy, cervical abnormalities, vaginal infections, and failure to establish a pregnancy. A review of the adverse events associated with vaginal bleeding does not

appear to indicate that either studied dose of Endometrin® resulted in intolerable or clinically significant bleeding in a majority of the subjects who were enrolled.

An additional concern for Endometrin® was the incidence of vaginal irritation, given the presence of adipic acid in the formulation. This was investigated using three methodologies:

- Colposcopy of the vaginal in the pharmacokinetic Study 2004-01
- Monitoring for vaginal irritation in the daily diaries in Study 2004-02
- Monitoring for adverse events and discontinuation secondary to vaginal irritation or lesions in Study 2004-02

Study 2004-01 did not reveal any pathological findings on colposcopy in any of the 48 subjects treated with 10 days of Endometrin®. In addition, no subjects in either of the pharmacokinetic studies (2004-01 or 2005-08) discontinued Endometrin® or had adverse events related to vaginal irritation. Finally, a review of the treatment-emergent adverse events and diary data on vaginal irritation, problems with intercourse and genital bleeding did not reveal that either studied dose of Endometrin® resulted discontinuations or serious adverse events related to vaginal irritation or lesions from Endometrin® use.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Controlled Study 2004-02 was used to estimate the incidence of adverse events in NDA 22-057/S-000 (The multiple dose studies 2004-01 and 2005-08 were open-label). The investigators were blinded to the treatment of subjects in Study 2004-02 to decrease bias and better determine whether the adverse events seen were related to the study medication. In the safety review, the source of the data has been identified in each section.

7.4.1.2 Combining data

No data were combined in NDA 22-057/S-000 as only one phase 3 study was submitted as the primary efficacy and safety database for Endometrin®.

7.4.2 Explorations for Predictive Factors

Study 2004-02 was not a large enough study to determine whether the different progesterone exposures during Assisted Reproductive Technology procedures resulted in statistically different differences in pharmacokinetics, pharmacodynamics or adverse event findings between active-treatment groups.

7.4.2.1 Explorations for dose dependency for adverse findings

The adverse findings in Study 2004-02 indicate that total adverse events and reproductive and breast disorders events are similar between the two dosage regimens for Endometrin®. The number of subjects with treatment-emergent adverse events in the Endometrin® three times daily dose group appears to be clinically similar to the active control group (Crinone®), and clinical similar between the two Endometrin® dose groups. An overview of this is seen in Table 38.

Table 38: Adverse events evaluated for dose dependency

Body System Adverse Event (AE)	Endometrin® 100 mg twice daily N=404	Endometrin® 100 mg three times daily N=404	Crinone® 8% gel once daily N=403
MedDRA preferred term			
Total number of subjects with at least one treatment related AE n(%)	215(53%)	217(54%)	210(52%)
Ovarian hyperstimulation syndrome	30(7%)	27(7%)	26(6%)
Vaginal hemorrhage	7(2%)	9(2%)	16(4%)
Uterine spasm	15(4%)	11(3%)	11(3%)
Metrorrhagia	6(1.5%)	5(1.2%)	6(1.5%)
Vulvovaginal discomfort	3(0.7%)	1(0.2%)	1(0.2%)
Vaginal burning or vaginal pain	1(0.2%)	4(1.0%)	2(0.8%)

Source: Adapted from NDA 22-057/S-000, Final Report for Study 2004-02, Table 14.3.1.2, pages 255 to 263 of 7469.

Reviewer's comments:

1. Study 2004-02 for Endometrin® does not demonstrate dose-dependency for reproductive and breast adverse events.
 2. The overall rate of vaginal bleeding events (adding events reported by MedDRA terminology of vaginal hemorrhage and metrorrhagia events together as a worst case scenario) was somewhat higher in the Crinone® treatment group (5.5%) compared to the other two Endometrin® treatment groups (3.2% in the Endometrin® twice daily group and 3.5% in the Endometrin® three times daily treatment group). The reason for this is unclear. Of interest, none of the reported events of vaginal bleeding were considered by the Investigator to be probably related to Endometrin® or Crinone® use.
- In conclusion, Study 2004-02 collected insufficient information to confirm whether a dose-dependent relationship for vaginal irritation or bleeding exists between the two Endometrin® dose groups. However, the lack of subjects that discontinued for vaginal bleeding or irritation after Endometrin® use and the lower overall rates of vaginal bleeding for the two Endometrin® groups are reassuring.

7.4.2.2 Explorations for time dependency for adverse findings

There was no evidence of any time dependency for any adverse findings, and therefore, no exploration for time-dependent adverse events was undertaken in the NDA submission.

7.4.2.3 Explorations for drug-demographic interactions

There was no evidence of drug-demographic interaction.

7.4.2.4 Explorations for drug-disease interactions

There was no evidence of drug-disease interaction.

7.4.2.5 Explorations for drug-drug interactions

There was no evidence of drug-drug interaction.

7.4.3 Causality Determination

In the primary phase 3 study, Study 2004-02, the reported SAEs (Did you intend to list the 3 serious adverse events) are unlikely to have been directly related to the use of progesterone inserts administered vaginally. The fourth SAE, pulmonary embolism is difficult to assign causality to the postoperative pulmonary embolism, as surgery is also a known risk factor for development of thrombotic events, although the estrogen may have been an additive factor. This concern will be addressed in labeling.

Other more serious adverse events that have been reported with other progesterone products include anaphylaxis were not seen in Study 2004-02, although the lack of reporting was more likely related more to the small study size, rather than the lack of causality. In fact, allergic reactions resulted in discontinuation of Endometrin®. Therefore, labeling will include that clinically significant allergic reactions were seen with use of Endometrin®.

For the more frequent but non-serious reproductive adverse events reported in Study 2004-02 (ovarian hyperstimulation syndrome) were roughly similar between the two Endometrin® dosing groups and will be reported in labeling.

b(4)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Two daily dosing regimens for the 100 mg Endometrin® inserts (twice daily and three times daily) were investigated in Study 2004-02. Both dosing regimens are recommended for approval for progesterone supplementation in infertile women undergoing Assisted Reproductive Technology procedures.

Reviewer's comment: As previously stated, 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.

8.2 Drug-Drug Interactions

No drug-drug interactions were uncovered during the clinical review process.

8.3 Special Populations

Endometrin® was investigated in women with infertility aged 19 to 42 years, inclusive. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic impairment.

No formal studies in humans on the effects of progesterone on reproduction or pregnancy were performed. Similarly, drug exposure in pregnant women was identified and pregnancy outcome information was followed and reported in Study 2004-02 by the Sponsor. An overview of this follow-up information is reviewed in Section 7.1.14.

8.4 Pediatrics

Endometrin® is not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

There were no advisory committee meetings in which Endometrin® was discussed.

8.6 Literature Review

Literature relevant to progesterone therapy has been referenced throughout the review as needed. The reviewer determined that there was no need for a separate comprehensive review of the literature on progesterone for luteal supplementation for subjects who will be undergoing Assisted Reproductive Technology procedures.

8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan for Endometrin®.

8.8 Other Relevant Materials

There are no other relevant materials that are not included in other sections of the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submitted clinical data from Study 2004-02 was adequate to determine the efficacy and safety of Endometrin® administered vaginally for the Division's proposed 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.

The primary efficacy variable for Study 2004-02 was ongoing pregnancy, defined as identification of fetal heart movement at 6 weeks of gestation after one Assisted Reproductive Technology cycle. The Sponsor set the non-inferiority criterion for Endometrin® relative to the approved comparator Crinone® at within 10% of the lower bound of a two-sided confidence interval. The efficacy findings in the Intent-to-treat population of Study 2004-02 concluded that:

- Endometrin® 100 mg twice daily dosing regime for luteal supplementation after Assisted Reproductive Technology procedures was non-inferior to Crinone®. This conclusion was based on the lower bound of the 95% confidence interval for the Endometrin® twice daily treatment group relative to the Crinone® treatment group of -10.3.
- Endometrin® 100 mg three times daily dosing regime was determined to be non-inferior to Crinone®. This conclusion was based on the lower bound of the 95% confidence interval for the Endometrin® three times daily treatment group relative to the Crinone® treatment group of -6.7.

Based on these efficacy findings, the reviewer recommends approval for both the Endometrin® 100 mg twice daily and three times daily dosing regimens for the indication of pregnancy through progesterone supplementation as a part of an Assisted Reproductive Technology program

b(4)

No new safety concerns arose during the conduct of Studies 2004-02, 2004-01 or 2005-08.

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends approval of both dosing regimens (100 mg twice daily and 100 mg three times daily) of progesterone inserts administered vaginally 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.

9.3 Recommendation on Postmarketing Actions

The reviewer recommends that a Phase 4 clinical study be conducted to establish efficacy, the appropriate dosing regimen and safety in women greater than or equal to age 35 up to age 45 for the indication of support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology treatment program for infertile women. The clinical study should also be designed as a non-inferiority comparison to

9.3.1 Risk Management Activity

There are no recommended post-marketing risk management activities.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

This reviewer recommends that a Phase 4 commitment to conduct a clinical study to establish efficacy, the appropriate dosing regimen and safety in women greater than or equal to age 35 up to age 45 as outlined in section 9.3 of this review.

9.4 Labeling Review

Labeling reviews were conducted by DMETS, DDMAC, the SEALD team and the Division. The Division's recommendation for labeling is attached to this review in section 10.2.

9.5 Comments to Sponsor

The reviewer notes that there were large discrepancies in the numbers of overall adverse events that were reported across the investigational sites. It is possible that some of this may be due to physician practice and different patient populations. However, this reviewer requests that for future studies you emphasize uniform reporting methods for adverse events to ensure standardization of capturing and reporting of all adverse events for ART studies across centers.

10 APPENDICES

10.1 Review of Individual Study Reports

The phase 3 Study 2004-02 is the primary subject of this review.

10.2 Line-by-Line Labeling Review

PLACE LABEL HERE.

11 REFERENCES

No additional references not previously noted are referenced in this review.

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

/s/

Audrey Gassman
6/20/2007 04:40:12 PM
MEDICAL OFFICER

Shelley Slaughter
6/20/2007 10:31:47 PM
MEDICAL OFFICER

I concur with Dr. Gassman's recommendation for Approval of
this application. I further concur with labeling recommendations.
See also TL memorandum

**Filing Memorandum
Division of Reproductive and Urologic Products**

NDA 22-057/S-000

Trade Name: Endometrin®
Generic Name: progesterone effervescent vaginal tablet
Sponsor: Ferring Pharmaceuticals, Inc.
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Classification: 3S
Submission Date: August 21, 2006
Indication: Pregnancy through progesterone supplementation as part of an Assisted Reproductive Technology (ART) program
Doses: 100 mg tablets administered vaginally twice daily and three times daily

Related Submission: IND 68,097
User Fee Goal Date: June 21, 2007
Team Leader Goal Date: April 21, 2007
Filing Meeting date: October 3, 2006
Preparer: Audrey Gassman, MD
Medical Officer
Division of Reproductive and Urologic Products

b(4)

Brief Regulatory History:

Endometrin® is a progesterone tablet to be used vaginally with an applicator for treatment of _____ women who are undergoing Assisted Reproductive Technology procedures. Endometrin® is an effervescent tablet containing micronized progesterone, and has been administered as a 100 mg tablet. Endometrin® is currently marketed in Israel and Hong Kong, and the Sponsor has proposed to market Endometrin® in the United States.

b(4)

The sponsor met with the Division for a pre-IND meeting on 23-Oct-03 to discuss the development of Endometrin®. The Division reviewed the outlines of chemistry and manufacturing information, non-clinical toxicology study proposals, a phase I/II pharmacokinetic protocol, and phase III clinical protocols. At the 23-Oct-03 meeting the Division recommended that the Sponsor submit the available detailed clinical study protocols for comment.

Teleconferences between the Sponsor and the Chemistry and Pharmacology/Toxicology Review Teams were held on June 28, 2004 and August 12, 2004, respectively to further discuss the development of Endometrin®.

- Study 2004-02 would only support the indication of luteal supplementation, not replacement
- The non-inferiority limit for study 2004-02 was defined as equal to or greater than 10%, and that the percentage of the difference of the lower limit of the 95% confidence interval needs to be reported to the first decimal point.
- The duration of use of Endometrin® needed to be reported in all subjects who became pregnant.
- The primary efficacy data set needs to include all subjects that received one dose or more of Endometrin®, whether or not they had embryo transfer.

No safety issues of concern are noted in the submission for Study 2004-02.

Twenty-six clinical sites were reported to have participated in Study 2004-02. Twenty five clinical sites enrolled subjects, one clinical site did not enroll subjects (Site #4). The number of subjects enrolled per clinical site ranged from 3 to 125. All financial disclosure forms were submitted, reviewed, and were found acceptable.

The request for a pediatric waiver under 21 CFR 314.55(c)(2) was included in the NDA 22-057/S-000 submission. A pediatric waiver was granted as there is no therapeutic use for Endometrin® in a pediatric population.

NDA 22-057/S-000 is submitted as a fully electronic submission in a modified eCTD format.

Fileability of NDA 22-057/S-000

NDA 22-057/S-000 is fileable.

Recommendations for a Division of Scientific Investigations Audit

The Division of Reproductive and Urologic Products requested a routine Division of Scientific Investigations audit for NDA 22-057 of three clinical sites on September 14, 2006.

Review of Financial Disclosure Documents

Form FDA 3454 (4/06), dated August 21, 2006 and signed by James H. Conover, Ph.D., Executive Director, Regulatory Affairs, Ferring Pharmaceuticals, Inc. was included in the submission. The submission contained financial disclosure documents for three submitted studies:

- For study 2004-01 (pharmacokinetic study), two clinical sites were listed. A review of the financial disclosure statements for the 2 Investigators or 9 sub-Investigators did not reveal any financial interests or were the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f).
- For study 2005-08 (pharmacokinetic), one study site was listed. A review of the financial disclosure statements for the investigator and sub-investigator did not

reveal any financial interests or that they were the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f).

- For the primary efficacy and safety study 2004-02, twenty-six clinical sites were listed in the submission (in section 1.3.4, the submission states that site #4 was skipped as no subjects were enrolled). A review of the financial disclosure statements for all 26 Investigators and 49 sub-Investigators did not reveal any financial interests or that they were the recipient of significant payment of other sorts as defined in 21 CFR 54.2(f). (Financial disclosure for site #10 submitted via fax on 04-Oct-06 and determined to be acceptable.)

Reviewer's Comments:

- **No Clinical Comments for the 74-day Filing Letter**
 - **Reviewer's Questions (#1 through #5) to be sent in a separate Advice/Information Letter:**
1. Please confirm that there are no outstanding regulatory actions or safety issues regarding Endometrin® in the countries overseas where the drug is currently approved and marketed.
 2. We note that the total number of AEs in Table 37 does not appear to match the AE dataset (in the SAS transport file) for study 2004-02 using the variable AETERM. Please check the total numbers of adverse events as listed in Table 37 against your SAS transport file AE dataset and make all corrections for all listed adverse events. Report the new percentages, and explain any new findings.
 3. Please provide a Summary Table for all adverse events > 1% for study 2004-02.
 4. Please provide a summary table of the number of serious adverse events by site and treatment group for study 2004-02. In addition, please provide a secondary summary table of the number of overall adverse events by site and treatment group similar to that outlined for subjects randomized in Section 10.1 Table 7.
 5. Please provide tables 14.2.5.1 through 14.2.5.10 (Live Birth Rate tables), 14.2.6.1 through 14.2.6.10 (Spontaneous Abortion Rate tables) and 14.2.7.1 through 14.2.7.10 (Elective Abortion Rates) as soon as possible for study 2004-02.
 6. Please provide tables 14.3.5.3.1 through 14.3.5.3.7 (Second Trimester Fetal Loss Rate tables), 14.3.5.4.1 through 14.3.5.4.7 (Third Trimester Fetal Loss Rate tables), 14.3.5.5.1 through 14.3.5.5.7 (Fetal Anomaly Rate tables) and 14.3.5.6.1 through 14.3.5.6.7. (Birth Defect Rate tables) for study 2004-02.

**Appears This Way
On Original**

**45 Day Filing Meeting Checklist
CLINICAL**

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	NA		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		(This information is not required)
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	X		
14) Has draft labeling been submitted?	X		(In the new PLR format as required)
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		

16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file: None.			

Appears This Way
On Original

Appears This Way
On Original

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

/s/

Audrey Gassman
10/4/2006 02:45:35 PM
MEDICAL OFFICER

Shelley Slaughter
10/4/2006 08:31:53 PM
MEDICAL OFFICER
I concur.