CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-057

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-057**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 21, 2006**
PRODUCT:	**Endometrin® 100 mg progesterone tablet**
INTENDED CLINICAL POPULATION:	**Women undergoing assisted reproduction therapy (ART)**
SPONSOR:	**Ferring Pharmaceuticals Inc.**
DOCUMENTS REVIEWED:	**Module 4**
REVIEW DIVISION:	**Division of Reproductive and Urologic Drug Products (HFD-580)**
PHARM/TOX REVIEWER:	**Leslie McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**John Kim, R. Ph., J.D.**

Date of review submission to Division File System (DFS): May 10, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approval

NDA 22-057 (Endometrin®, 100 mg progesterone tablet) has been submitted by Ferring Pharmaceuticals, Inc. for use in women undergoing Assisted Reproductive Technology (ART). It is administered vaginally two or three times daily to provide progesterone supplementation to the endometrium, with the aim of promoting establishment of pregnancy.

B. Recommendation for nonclinical studies : none

Characterization of the nonclinical pharmacology and toxicology of Endometrin® is adequate.

C. Recommendations on labeling:

Under the new Physician's Labeling Rule, the label is required to have a Pharm/Tox section (item #13). The following wording is suggested for the Pharm/Tox section to cover carcinogenesis, mutagenesis, and fertility.

"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."

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The nonclinical toxicology of progesterone is well understood. Because progesterone has been well studied in animals and humans, and its effects are considered general knowledge, no new repeat-dose toxicity, genotoxicity, carcinogenicity, or reproductive and developmental nonclinical studies were submitted.

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

B. Pharmacologic activity

The pharmacological properties of Endometrin® are the same as oral progestins. The main difference between vaginally applied and oral progesterone is the pharmacokinetic profile. Vaginally absorbed progesterone primarily acts locally; first-pass metabolism in the gut wall and the liver is largely avoided.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

Appears This Way
On Original

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

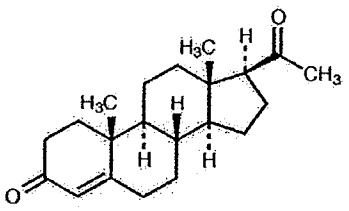
NDA number: 22-057
Review number: 1
Sequence number/date/type of submission: 000 / Aug. 21, 2006 / 505(b)1
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Ferring Pharmaceuticals, Inc., Suffern, NY, USA b(4)
Manufacturer for drug substance: ⌜

⌟

Reviewer name: Leslie McKinney, PhD
Division name: Division of Reproductive and Urologic Drugs
HFD #: 580
Review completion date: Feb. 9, 2007

Drug:

Trade name: Endometrin®
Generic name: progesterone
Code name: none
Chemical name: pregn-4-ene-3, 20-dione
CAS registry number: 57-83-0
Molecular formula/molecular weight: $C_{21}H_{30}O_2$ / 314.46
Structure:



Relevant INDs/NDAs/DMFs: DMF ⌜ ⌟ progesterone USP/EP b(4)
NDA 20-701 and 20-756, Crinone® vaginal gel

Drug class: steroid hormone

Intended clinical population: Women undergoing assisted reproductive technology (ART) treatment who require progesterone supplementation.

Clinical formulation: Effervescent tablet containing 100 mg micronized progesterone. All of the excipients listed are FDA-approved. Toxnet databases were reviewed for adipic acid and polyvinylpyrrolidone, since these excipients were present at relatively high concentrations. Both compounds have benign toxicity profiles (see Kennedy, Jr., GL, Toxicity of adipic acid, Drug Chem Toxicol 25(2):191 (2002) and polyvinylpyrrolidone monograph published in the WHO Food Additives Series 15; www.inchem.org/documnets/jecfa/jecmono/v15je08.htm).

Ingredient	Function	Supplier	mg/tablet
Progesterone, USP (micronized)	Active ingredient		100.0
Colloidal silicone dioxide, NF			
Lactose Monohydrate, NF			
Pregelatinized starch, NF			
Polyvinylpyrrolidone, USP			
Adipic acid, FCC			
Sodium bicarbonate, USP			
Sodium lauryl sulfate, NF			
Magnesium stearate, NF			
Total			1250.0

b(4)

Information in this table combined from sponsor's Table A, 2.3.P.1, p 4 of CMC section and Table A, 2.3.P.3.

Lot comparison: The batch analysis for the three lots used in the clinical study (see Module 2, CMC section) was compared to the analysis of the lots used for the nonclinical studies (see Dose Formulation Sample Analysis under individual study reports). The lots were analytically comparable. Any impurities are therefore considered qualified.

Impurities/degradants: The sponsor states that the only significant impurity/degradant present in the drug product was ——— , which ranged from —— % and did not increase over time up to 18 months. A search of Toxnet revealed no entries for ——— , which is structurally closely related to progesterone. b(4)

Study title	Study #	Drug product Batch #	COA?	Drug substance manufacturer	Formulation
A primary irritation study in rabbits with Endometrin®	3662.2	F-671-029	yes	received by test laboratory from sponsor	100 mg progesterone/ 1.25 g powder
A dermal sensitization study in guinea pigs with Endometrin®	3662.3	F-671-029	yes	received by test laboratory from sponsor	100 mg progesterone/ 1.25 g powder
A 14-day vaginal irritation-toxicity study in rabbits with Endometrin®	3662.4	F-671-029	yes	received by test laboratory from sponsor	100 mg progesterone/ 1.25 g powder
A 90-day vaginal irritation-toxicity study of Endometrin® in rabbits.	XHM00008	F-965-022	yes	received from Pharmaceutics International, Inc., Hunt Valley, MD	common blend (pre-compressed clinical formulation)

Lot numbers used for clinical trials (sponsor's Table A, 2.3.R)

	Tablet lot # (MPR*0804)	Blend lot# (MPR 0802)	API Granulation lot# (MPR 0801)	API lot#	Clinical study #
Batch 1	0804.001	0802.002	0801.002	04-0028	2004-01
Batch 2	0804.005	0802.004 0802.005	0801.005 0801.006	04-0465 04-0466	2004-02
Batch 3	0804.006	0802.005	0801.006	04-0466	2004-02

*Master Production Record

Route of administration: Administered vaginally b.i.d. or t.i.d.

Background:

Progesterone is a well-studied human hormone whose pharmacological and toxicological profiles are well-known. Vaginal routes of delivery are useful for various indications because they avoid the hepatic first-pass effect and provide high endometrial levels while maintaining low serum levels. The advantage of targeted delivery and ease of use is the rationale behind the development of vaginal progesterone products.

The rationale for the use of progesterone in assisted reproductive technology is that supplemental progesterone may promote maintenance of the endometrium during the luteal phase and enhance the likelihood of implantation of a fertilized egg. Supplementation in progesterone-deficient women is targeted to produce normal mid-luteal progesterone levels in the range of 10 ng/mL. Vaginal application of progesterone is proposed to be an effective way of delivering progesterone to the target organ (uterus) without significantly increasing systemic exposure. Endometrin® is approved and marketed for ART in Israel and Hong-Kong since 2003.

Studies fully reviewed within this submission:

Study Title	Study # and Volume	Conducting laboratory and location	GLP + QA
A 14-day vaginal irritation-toxicity study in rabbits with Endometrin®	Study #3662.4 Module 4: Section 4.2.3.2.1	[redacted]	yes + yes
A 90-day vaginal irritation-toxicity study of Endometrin® in rabbits.	Study #XHM00008 Module 4: Section 4.2.3.2.2	[redacted]	yes + yes

b(4)

Studies reviewed in summary form within this submission:

Study Title	Study # and Volume	Conducting laboratory and location	GLP + QA
A primary skin irritation study in rabbits with Endometrin®	Study # 3662.2 Module 4: Section 4.2.3.1.1	[redacted]	yes + yes
A dermal sensitization study in guinea pigs with Endometrin®	Study # 3662.3 Module 4: Section 4.2.3.7.1.1	[redacted]	yes + yes

b(4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Progesterone is a steroid hormone produced primarily by the ovary during the luteal phase of the menstrual cycle. Target organs include the uterus, vagina, breast, and brain. It plays a critical role in maturation of the endometrium and the establishment and maintenance of pregnancy.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Progesterone acts by binding to the nuclear progesterone receptor (PR), which subsequently regulates transcription of various genes in response to progesterone binding. There are two isoforms of the PR, PR-A and PR-B, which mediate different actions of progesterone in target tissues.

Drug activity related to proposed indication:

ART involves harvesting of oocytes and in vitro fertilization (IVF) with donated sperm, followed by implantation of the embryo into the uterus. For implantation to be successful and pregnancy to be established, the endometrium must be differentiated to its secretory form, which is induced by progesterone. While some endogenous progesterone is available during a cycle of IVF, the process of harvesting oocytes may lead to a relative deficit of progesterone. Thus, progesterone supplementation, by either the oral or vaginal route, has become routine in the practice of ART.

2.6.2.3 Secondary pharmacodynamics

Progesterone causes proliferation of acini of the mammary gland and also has various metabolic effects.

2.6.2.4 Safety pharmacology

Because there is extensive clinical experience with progestins, nonclinical safety studies were not carried out for Endometrin®.

2.6.2.5 Pharmacodynamic drug interactions

Again, because relevant human data are available for drug interactions with progesterone, nonclinical studies were not carried out for Endometrin®.

2.6.3 PHARMACOLOGY TABULATED SUMMARY N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

There were no nonclinical studies carried out specifically to study the pharmacokinetics of Endometrin®. Plasma levels of progesterone were, however, measured as part of the 14-day repeat-dose study to establish adequate systemic exposure following vaginal administration in rabbits (see 2.6.6.3). Following intravaginal administration in rabbits, increases in plasma levels

were seen, with maximal levels recorded 1-2 hours post-administration. At a dose comparable to the human dose based on mg/kg, the Cmax was comparable to the normal mid-luteal progesterone levels in women (~10 ng/ml).

2.6.4.2 Methods of Analysis: N/A

2.6.4.3 Absorption: N/A

2.6.4.4 Distribution: N/A

2.6.4.5 Metabolism: N/A

2.6.4.6 Excretion N/A

2.6.4.7 Pharmacokinetic drug interactions N/A

2.6.4.8 Other Pharmacokinetic Studies N/A

2.6.4.9 Discussion and Conclusions N/A

2.6.4.10 Tables and figures to include comparative TK summary: N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The only non-clinical studies required for vaginally administered Endometrin® were topical and vaginal irritation studies to determine the local tolerability of the final drug product. To support the NDA, the sponsor carried out 4 studies:

1) a primary irritation study in rabbit
2) a dermal sensitization study in guinea pig
3) a 14-day vaginal irritation-toxicity study in rabbits
4) a 90-day vaginal irritation-toxicity study in rabbits

Each of these studies showed minimal findings of toxicity, as summarized below.

2.6.6.2 Single-dose toxicity N/A

2.6.6.3 Repeat-dose toxicity

Study title: A 14-day vaginal irritation-toxicity study in rabbits with Endometrin®.

Key study findings: There was no mortality or sign of systemic toxicity in this study. Vaginal irritation ratings were minimal on the basis of histopathology. This study covered a dose range of 1.6-14.4 mg/kg Endometrin®, which corresponded to 6.4-57.6 mg progesterone per animal. These doses cover multiples of ~1 – 10X the human dose on a mg/kg basis.

Study no. 3662.4
Volume #, and page #: Module 4: Section 4.2.3.2.1
Conducting laboratory and location: [redacted] b(4)
Date of study initiation: 1-23-04
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: Endometrin®, identified as lot # F-671-029, 101.9%

Methods

Doses: 0 (separate saline and placebo controls), 1.6, 4.8, 9.6, 14.4 mg/kg Endometrin® which corresponded to 6.4, 19.2, 38.4, 57.6 mg progesterone, twice daily
Species/strain: New Zealand white rabbits
Number/sex/group or time point (main study): 5 F
Route, formulation, volume, and infusion rate: vaginal, powder in saline (saline-slurry), 1.2 mL volume
Satellite groups used for toxicokinetics or recovery: TK samples drawn from ear vein
Age: 25-26 weeks
Weight: 3.9-4.5 kg
Sampling times: TK taken at prior to and 1, 2, 4, and 7 hrs post-AM dose on days -2, 1, 7, and 13; an additional sample was taken on day 7 midway between the AM and PM doses.

Observation and Times:

Clinical signs: daily on days -1 to 14
Body weights: on days -1, 7, 14
Gross pathology: at necropsy
Histopathology: vulva, vagina (cranial, middle, and caudal), cervix, uterus, oviducts, ovaries, urinary bladder, urethra, iliac and inguinal lymph nodes at necropsy

Results:

Mortality: none
Clinical signs: sporadic incidence of few feces, decreased food consumption
Body weights: slight body weight loss in individual animals scattered across groups
Gross pathology: no test-article related findings
Histopathology: composite average scores for vaginal irritation in all groups were 2-4 and were not dose-dependent. No individual score was higher than 7. The vaginal irritation scoring system is as follows:

Composite average score:	1-4	Minimal irritation	Acceptable
	5-8	Mild irritation	Acceptable
	9-11	Moderate irritation	Borderline
	12-16	Marked irritation	Unacceptable

Toxicokinetics: Mean plasma progesterone Cmax and AUC_{last} for treated animals were markedly higher than for control animals, demonstrating that systemic exposure to progesterone was achieved. Cmax values increased in a less than dose proportional manner,

and were lower at day 13 than at day 0. Likewise, AUC values increased in a less than dose-proportional manner and were lower at day 13 than at day 0. T_{max} ranged from 1-2 hrs.

Summary of Mean[a] Progesterone Plasma Toxicokinetic Parameters

Dosage (mg/kg)	Group	C_{max} (ng/mL)	t_{max} (h)	t_{last} (h)	AUC_{last} (ng-h/mL)	AUC (ng-h/mL)	$t_{1/2}$ (h)
Day 0							
0	1	1.13	1[b]	2[b]	0.635	NE	NE
1.6	3	21.7	1	7	57.7	73.3[c]	1.6[c]
4.8	4	41.2	1	7	156	484[b]	6.6[b]
9.6	5	43.2	1	7	206	335[b]	3.3[b]
14.4	6	49.4	2	7	243	62.2[d]	1.1[d]
Day 13							
0	1	<LOQ	NA	NA	0	NE	NE
1.6	3	11.9	1	7	28.6	39.6[b]	1.5[b]
4.8	4	14.5	1	7	61.3	63.9[e]	4.4[e]
9.6	5	16.0	1	7	58.9	117[c]	3.3[c]
14.4	6	34.1	2	7	174	42.0[d]	3.7[d]

NE: Not estimated.
LOQ: Limit of quantitation of 0.2 ng/mL.
NA: Not applicable.
a: Median for t_{max} and t_{last}; n=5.
b: n=3.
c: n=4.
d: n=1.
e: n=2.

C_{max} and t_{max} were obtained by inspection. AUC was estimated using the linear trapezoidal rule. AUC_{last} represented the area through the time (t_{last}) of the last measured concentration (C_{last}), which was at 7 hrs post-dose. AUC extrapolated to infinity (AUC) was estimated by adding AUC_{last} and the ratio of C_{last}/λ, where λ is the terminal rate constant.

Study title: A 90-day vaginal irritation-toxicity study of Endometrin® in rabbits.

Key study findings: One female was found dead on day 26 belonging to dosing group 9.6 mg/kg (mid-dose). Findings included fluid and edema in the abdomen, left kidney and uterine horn agenesis, and enlarged right kidney. Death was ruled not test-article related. Vaginal tissues were examined histologically and scored for irritation. Group mean irritation scores were 2.3, 3.6, 4.1, 3.9, and 3.4 for dosing groups 1-5 respectively, which corresponded to ratings of acceptable minimal irritation. No animals were observed to have erosions. No other treatment-related microscopic findings in vaginal tissues were reported. The doses covered the range of approximately 3.4, 6.7 and 10X the HED for a single 100 mg progesterone tablet.

Study no. XHM00008
Volume #, and page #: Module 4: Section 4.2.3.2.2
Conducting laboratory and location: [redacted] b(4)
Date of study initiation: 8-19-04

GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: Endometrin® common blend (pre-compressed clinical formulation) lot # F-965-022, 98.4%
Methods
Doses: 0 (saline and placebo control groups), 4.8, 9.6, 14.4 mg/kg progesterone which corresponds to 19.2, 38.4, 57.6 mg progesterone per animal, twice daily
Dosing groups designated 1-5 (saline, placebo, low, mid, and high dose).
Species/strain: New Zealand white rabbits
Number/sex/group or time point (main study): 10 F
Route, formulation, volume, and infusion rate: vaginal, test article in saline, 1.2 mL
Satellite groups used for toxicokinetics or recovery: none
Age: >25 weeks
Weight: ≥ 3.5 kg

Observation and Times:
Clinical signs: 2X daily; detailed observations weekly and prior to necropsy
Body weights: weekly
Food consumption: daily
Ophthalmoscopy: prior to 1st dose and just prior to necropsy
Hematology: pre-test and at end of study, standard panel
Clinical chemistry: pre-test and at end of study, standard panel
Urinalysis: pre-test and at end of study, standard panel
Gross pathology: at necropsy, standard panel
Organ weights: at necropsy, standard panel
Histopathology: standard battery fixed and stored; vaginal tract tissues analyzed for irritation

Results:

Mortality: one female found dead on day 26; dosing group 9.6 mg/kg; fluid and edema in the abdomen, left kidney and uterine horn agenesis and enlarged right kidney. Death ruled not test-article related. Reviewer agrees.
Clinical signs: no test-article related changes
Body weights: no test-article related changes
Food consumption: no test-article related changes
Ophthalmoscopy: no test-article related changes
Hematology: no test-article related changes
Clinical chemistry: LDH was statistically increased in groups 3 and 5 at the end of the study, but values were within the pre-test range. Not considered test-article related.
Urinalysis: no test-article related changes
Gross pathology: abnormal content of the vaginal tract likely due to repeat administration of pasty material; urinary bladder findings included foci in the placebo, edema and thickened mucosa at all three treatment doses.
Organ weights: no test-article related changes
Histopathology: Vagina: group mean irritation scores were 2.3, 3.6, 4.1, 3.9, and 3.4 for Groups 1-5 respectively, which corresponded to ratings of acceptable minimal irritation. The vaginal irritation scoring system is as follows:

Composite average score:	1-4	Minimal irritation	Acceptable
	5-8	Mild irritation	Acceptable
	9-11	Moderate irritation	Borderline
	12-16	Marked irritation	Unacceptable

No animals were observed to have erosions. No other treatment-related microscopic findings in vaginal tissues were reported. Bladder: Mixed cell inflammation present in control and treated groups.

2.6.6.4 Genetic toxicology N/A

2.6.6.5 Carcinogenicity N/A

2.6.6.6 Reproductive and developmental toxicology N/A

2.6.6.7 Local tolerance

A primary skin irritation study in rabbits with Endometrin®
Study # 3662.2
Module 4: Section 4.2.3.1.1

Six New Zealand white rabbits, each with 2 intact and 2 abraded one inch square sites, received 0.5 g doses of Endometrin® (~ 40 mg progesterone) or placebo as single dermal applications. (One 100 mg tablet of Endometrin® ~1.25 g.) Doses were held in contact with the skin under a patch for 24 hours, which was then removed and the skin cleaned. Test sites were scored for dermal irritation for up to 72 hrs following patch removal.

Exposure of Endometrin® to intact skin produced very slight erythema on 6/6 test sites and very slight edema on 3/6 test sites at the 1 hr scoring interval. Dermal irritation resolved by the 48-hr scoring interval.

Exposure of Endometrin® to abraded skin produced very slight to slight erythema on 6/6 test sites and very light edema on 1/6 test sites at the 1 hr scoring interval which resolved by the 72-hr scoring interval.

Exposure of placebo to either intact or abraded skin produced very slight erythema on 6/6 test sites at 1 hr. Dermal irritation resolved by 48 hrs in intact skin and 72 hrs on abraded skin.

There were no other clinical signs. Endometrin® was thus considered to be a nonirritant. The Primary Irritation Indices (PII) for Endometrin® and placebo were 0.75 and 0.54, similar to each other, and there were no significant differences between the intact and abraded test sites.

2.6.6.8 Special toxicology studies

A dermal sensitization study in guinea pigs with Endometrin®
Study # 3662.3
Module 4:Section 4.2.3.7.1.1

10 male and 10 female Hartley-derived albino guinea pigs were topically treated with 0.3 g doses of Endometrin® (~24 mg progesterone) 3X/wk for 3 consecutive weeks, for a total of 9

induction exposures. 5 males and 5 females were treated with placebo. Following a 2-week rest period, a challenge was performed whereby the 20 test, 10 placebo and 10 naïve (common challenge control) guinea pigs were topically treated with Endometrin® and/or placebo. Challenge responses in the test and placebo animals were compared with those of the naïve control animals. Following challenge, dermal reaction scores were 0 in all test, placebo, and naïve animals at the 24 and 48-hr scoring intervals. Group mean dermal scores were 0.0 in the test, placebo, and common challenge control animals. Based on these results, Endometrin® or its placebo are considered to be contact non-sensitizers in guinea pigs.

Group	# animals	Phase/Treatment	
		Induction 1-9	Challenge
Test	20	Endometrin®	Endometrin®
Placebo	10	Placebo	Placebo
Common challenge control	10	----	Endometrin® and placebo

2.6.6.9 Discussion and Conclusions

Toxicology studies designed to address whether there are any novel toxicities of Endometrin® administered by the vaginal route of administration yielded no significant signs of systemic or local toxicity.

2.6.6.10 Tables and Figures N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Study title	Study #	Doses	Duration of dosing	Route of administration/ formulation	Result
A primary irritation study in rabbits with Endometrin®	3662.2	0.5 g Endometrin® /site	24 hrs	Topical / powder moistened with saline	Found to be a non-irritant
A dermal sensitization study in guinea pigs with Endometrin®	3662.3	0.3 g Endometrin® /site	3 week induction followed by rest/challenge	Topical / powder moistened with saline	Found to be non-sensitizing
A 14-day vaginal irritation-toxicity study in rabbits with Endometrin®	3662.4	1.6, 4.8, 9.6, 14.4 mg/kg progesterone	b.i.d. 14 days	Vaginal / powder dissolved in saline	Vaginal irritation rated minimal
A 90-day vaginal irritation-toxicity study of Endometrin® in rabbits.	XHM00008	4.8, 9.6, 14.4 mg/kg progesterone	b.i.d 90 days	Vaginal / powder dissolved in saline	Vaginal irritation rated minimal

Table constructed by the reviewer. Note that a 1.25 g Endometrin® tablet contains 100 mg progesterone.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Vaginally administered Endometrin® induced no novel systemic or local toxicities. The doses tested exceeded the likely human exposure by up to a factor of 10 and were well tolerated. Taken together, animal studies and prior clinical experience with the product indicate that Endometrin® is reasonably safe to use for the proposed ART indication.

Unresolved toxicology issues (if any): None

Recommendations: From a Pharm/Tox perspective, this NDA can be approved.

Suggested labeling:

Class labeling for progestins. Under the new Physician's Labeling Rule, the label is required to have a Pharm/Tox section (Item #13). The following wording is suggested for the Pharm/Tox section to cover carcinogenesis, mutagenesis, and fertility.

> "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."

APPENDIX/ATTACHMENTS: NONE

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

/s/

Leslie McKinney
5/11/2007 06:50:30 PM
PHARMACOLOGIST

Lynnda Reid
5/14/2007 09:55:41 AM
PHARMACOLOGIST

45 Day NDA Meeting Checklist
Pharmacology/Toxicology

NDA Number: 22-057 **Date:** Sept. 20, 2006
Drug Name: Endometrin® **Reviewer:** Leslie McKinney, Ph.D.
Sponsor: Ferring Pharmaceuticals, Inc.

Date CDER Received: August 21, 2006
Filing Date: October 20, 2006
User Fee Date: June 21, 2007
Expected Date of Draft Review: December 20, 2006

On initial overview of the Pharm/Tox portion of the NDA application

1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	yes	
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	yes	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?	yes	
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	yes	
5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	no	The formulation given for the clinical and non-clinical batches are identical. The impurity profiles for the clinical and nonclinical batches are closely comparable.

6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	yes	
7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	yes	
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	yes	submitted studies were GLP
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	yes yes yes	There was no Pharm/Tox section in the label.
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	yes	
11)	Reasons for refusal to file:		

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/s/

Leslie McKinney
10/4/2006 02:52:26 PM
PHARMACOLOGIST

Lynnda Reid
10/4/2006 04:57:36 PM
PHARMACOLOGIST