

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-057**

**PROPRIETARY NAME REVIEW(S)**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
(DMETS; WHITE OAK 22, MAILSTOP 4447)**

<b>DATE RECEIVED:</b> August 29, 2006	<b>DESIRED COMPLETION DATE:</b> November 28, 2006 <b>PDUFA DATE :</b> June 21, 2007	<b>OSE CONSULT #'s:</b> 2006-131, 2006-132, and 2006-869
<b>TO:</b> Scott Monroe, M.D. Acting Director, Division of Reproductive and Urologic Products HFD-580		
<b>THROUGH:</b> Nora Roselle, Pharm D, Team Leader Denise Toyer, Pharm D, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support, HFD-420		
<b>FROM:</b> Richard Abate, RPh, MS, Safety Evaluator Division of Medication Errors and Technical Support, HFD-420		
<b>PRODUCT NAME:</b> <b>Endometrin</b> (Progesterone Vaginal Insert) 100 mg	<b>NDA SPONSOR:</b> Ferring Pharmaceuticals	
<b>NDA#: 22-057</b>		
<b>RECOMMENDATIONS:</b> 1. DMETS has no objections to the use of the proprietary name, Endometrin. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. 2. DMETS recommends consulting Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), for the proper designation of the established name. 3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product. 4. DDMAC finds the proprietary name Endometrin acceptable from a promotional perspective.  DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Jenna Lyndly, project manager, at 301-796-2224.		

Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
White Oak 22, Mail Stop 4447  
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

**DATE OF REVIEW:** September 21, 2006  
**NDA#:** 22-057  
**NAME OF DRUG:** **Endometrin**  
(Progesterone Vaginal Insert)  
100 mg  
**NDA HOLDER:** Ferring Pharmaceuticals

**I. INTRODUCTION:**

This consult was written in response to requests from the Division of Reproductive and Urologic Products (HFD-580), for assessment of the proprietary name "Endometrin" regarding potential name confusion with other proprietary or established drug names and for safety assessment of the container label and carton labeling. Container labels, carton, patient, and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Endometrin contains Progesterone in an effervescent tablet for vaginal administration. Endometrin is being developed for progesterone supplementation in women undergoing assisted reproductive treatment (ART). The recommended dose is 100 mg administered vaginally two or three times daily.

⌞  
⌞ Endometrin will be supplied as a box containing 21 — unit dose tablets and polyethylene vaginal applicators.

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**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to Endometrin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. The Saegis<sup>6</sup>

<sup>1</sup> MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Phonetic and Orthographic Computer Analysis (POCA)

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a product must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Endometrin. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Endometrin, acceptable from a promotional perspective.
2. The Expert Panel identified eleven proprietary or established names that were thought to have the potential for confusion with Endometrin. Of these eleven names, eight were not reviewed further due to the lack of significant look-alike and/or sound-alike similarities with Endometrin, in addition to differentiating product characteristics that may include: the product strength, indication for use, frequency of administration, route of administration, dosage formulation, therapeutic class, storage conditions, patient population, prescriber population, product unavailability and/or type of marketing or distribution. The names not reviewed are as follows: Emedastine, Enalapril, Endo-Avitene, Endotelon (France), Endothelin, Erythrocin, Indomecin (Columbia), and Prometrium. The three remaining product names that warrant further analysis are listed in Table 1 (see below and page 4) along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Proprietary Name	Dosage forms, Established name	Usual adult dose	Other
Endometrin	Progesterone Vaginal Insert: 100 mg	Insert one insert, 100 mg, vaginally twice or three times daily	
Indomethacin (established name for Indocin, generic available)	Indomethacin Capsules: 25 mg, 50 mg Suppositories: 50 mg Oral Suspension: 5 mg/mL  Extended Release Capsules: 75 mg	25 - 50 mg by mouth or rectally twice daily to three times daily, up to maximum of 200 mg daily.  1 capsule once or twice daily.	LA/SA

Proposed Name	Dosage Form(s), Established Name	Usual Adult Dose(s)	Other
Endometrin	Progesterone 20mg, 100mg, 150mg	Insert one insert 200 mg vaginally twice or three times daily	
Ondansetron (established name for Zofran)	Ondansetron Hydrochloride Tablets: 4 mg, 8 mg, and 24 mg Oral Disintegrating Tablets: 4 mg and 8 mg Oral Solution: 4 mg/5 mL  Injection: 2 mg/mL Premixed Injection: 32 mg/50 mL	4 - 24 mg orally 30 minutes prior to emetogenic chemotherapy.  0.15 mg/kg IV 30 minutes before and repeated at 4 and 8 hours or 32 mg IV 30 minutes prior to chemotherapy.	LA
Endometril (foreign)	Lynestrenol Tablets: 5 mg	1-2 tablets daily.	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Endometrin with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Endometrin (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: <i>Endometrin 100mg</i> <i># 90</i>  <i>Insert Vaginally TID</i>	Endometrin 100 mg # 90 Insert one vaginally three times daily.
Inpatient RX: <i>Endometrin 100mg Insert Vaginally tid</i>	

### 2. Results:

One respondent from the inpatient written study interpreted the proposed name as Endomethacin. Endomethacin sounds and looks similar to the currently marketed product

Indomethacin. See Appendix A for the complete listing of interpretations from the verbal and written studies.

### C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Endometrin, the primary concerns relating to look-alike and sound-alike confusion were Indomethacin, Ondansetron, and Endometril. It was also noted that the proposed name looks and sounds like several medical terms. DMETS also had concerns with the proposed established name.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with the aforementioned names. However, one respondent from the written inpatient study interpreted this name as Endomethacin which is similar in appearance and sound to Indomethacin. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Endometrin.

#### 1. Look- and Sound-Alike Names of Concern

- a. Indomethacin was identified as having look-alike and sound-alike similarities to the proposed name, Endometrin. Indomethacin is a non-steroidal anti-inflammatory medication used for moderate to severe arthritis. The usual dose of Indomethacin is 25 mg to 50 mg twice or three times daily.

Endometrin looks and sounds similar to Indomethacin. The first seven letters in each name are almost identical, "endomet" versus "indomet," when written and spoken aloud. Similarly, both names end with "in". However, the endings of each name ("rin" vs. "hacin") and the additional length of Indomethacin help differentiate one name from the other.

*indomethacin*  
*endometrin*

While both Endometrin and Indomethacin will be primarily used as outpatient therapies, share an overlapping frequency of administration (bid to tid), numeral dose (**one** tablet vs. **one** capsule or **one** suppository), and similar patient instructions for use (insert one bid or tid), the two drugs have many differentiating characteristics. Differences include strength (100 mg vs. 25 mg, 50 mg, 75 mg and 5 mg/mL), route of administration (vaginal vs. oral and rectal), dosage form (effervescent tablet vs. capsule, suppository, and oral suspension), indication of use (prepare uterus for pregnancy and supplement progesterone during first trimester of pregnancy in women undergoing ART vs. arthritis), and prescribing population (reproductive specialists vs. general practitioners). Patients prescribed Endometrin will likely be well educated how to use this product as it is to be used in conjunction with various assisted reproductive treatment regimens which require consistent follow-up with a physician. While these products look and sound-alike, DMETS believes the differing product characteristics, including specialized prescriber and patient populations for Endometrin, will help minimize the potential for confusion between these two products.

- b. Ondansetron was identified as having look-alike similarities to Endometrin. Ondansetron, the established name for Zofran, is indicated for the prevention of chemotherapy induced nausea and vomiting and to prevent or treat post operative nausea and vomiting. The usual dose of Ondansetron for chemotherapy induced nausea and vomiting is 8 to 24 mg orally or 32 mg IV as a single dose. The dose for post-operative nausea and vomiting is 4 mg IV every 4 hours.

Endometrin and Ondansetron have some orthographic similarity. The beginnings of each name, “endom” and “ondan,” are orthographically similar as are the endings (“trin” vs. “tron”). However, when scripted, the middle two letters, “se,” in Ondansetron slightly increase the length and look of the name when compared to the middle letter “e” in Endometrin.



Endometrin and Ondansetron share overlapping characteristics. These include the dosage form (tablet), numeric dose (one tablet), and use in the outpatient setting. Similarly, Ondansetron is commonly prescribed for hyperemesis gravidarum providing common patient and prescribing populations with Endometrin. However, there are several differentiating product characteristics between Endometrin and Ondansetron. Differences include: strength (100 mg vs. 4 mg, 8 mg, 24 mg, 4 mg/5 mL, 2 mg/mL and 32 mg/50 mL), route of administration (vaginal vs. oral and injection), indication of use (prepare uterus for pregnancy and supplement progesterone during first trimester of pregnancy in women undergoing ART vs. nausea and vomiting), and duration of therapy (several weeks vs. one to several days). While the dose may overlap (one tablet), Ondansetron is available in multiple strengths and dosage forms. Therefore, the strength and dosage form would need to be indicated on a prescription order. In addition, patients prescribed Endometrin will likely be well educated how to use this product as it is to be used in conjunction with various assisted reproductive treatment regimens which require consistent follow-up with a physician. While these products have look-alike similarities, DMETS believes the differing product characteristics will help minimize the potential for confusion between these two products.

- c. Endometril was identified as having look- and sound-alike characteristics with Endometrin. Endometril (Lynestrenol) is a progestin marketed in Eastern Europe and Indonesia for endometriosis, amenorrhea and premenstrual syndrome. The usual dose is 5 to 10 mg daily.

The names Endometrin and Endometril both share the same nine letters “endometri.” The final letter “n” in Endometrin compared to the upstroke of the “l” in Endometril provides some orthographic differentiation when scripted. In addition, the “n” in Endometrin compared to the “l” in Endometril also provides some phonetic differentiation when pronounced.

Endometril  
Endometrin

Endometrin and Endometril share the following product characteristics: dosage form (tablet), dose (one tablet), prescriber (OB/GYN's), patient population (women), and therapeutic class (progestins). However, Endometrin and Endometril differ in route of administration (vaginal vs. oral), strength (100 mg vs. 5 mg) and frequency of administration (bid to tid vs. daily). Due to the fact that Endometril is a foreign drug marketed outside the United States, DMETS believes there is decreased risk for confusion between these products.

2. Other Concerns with the Proposed Name

Endometrin looks and sounds like the following medical terms: endometrial, endometrium, and endometriosis. Progesterone has pharmacologic effects on the endometrium to maintain pregnancy. The name Endometrin may imply that it is indicated for the condition of endometriosis. While it is a progestin, it is not intended for the treatment of endometriosis. Instead, it is indicated to prepare uterus for pregnancy and supplement progesterone during first trimester of pregnancy in women undergoing ART. The name could be considered misleading as some prescribers, unfamiliar with this product, may think the intended indication of use for Endometrin is endometriosis. However, the specialized indication of Endometrin will likely lead prescribers, unfamiliar with this product, to consult a drug reference prior to prescribing. DMETS believes the additional information of dose, frequency of administration, and route of administration appearing with Endometrin may reduce confusion with these medical terms.

3. Established Name Issues

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III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton, patient, and insert labeling of Endometrin, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. DMETS notes the sponsor proposes — a 21 — tablet package. The frequency of administration for Endometrin is two or three times daily. The package of 21 tablets will provide a week's supply for three times daily frequency. ┌

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┌ The amount dispensed will likely be by the number of boxes or tablets (e.g. one box or 21 tablets ——— ). DMETS recommends that this product be placed in unit of use packages (i.e. cartons of 14 tablets and 21 tablets) to avoid potential errors.

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B. BLISTER LABEL ┌

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1. According to 21 CFR 201.10(g)(2), the established name should be at least ½ the size of the proprietary name. As presented, the established name is too small. Revise accordingly to increase the size and prominence.
2. DMETS recommends the strength appears outside the parentheses and follow the established name to allow more prominence of this information. Presentation should read as follows:

Endometrin  
(Progesterone Vaginal Insert)  
100 mg

Additionally, the font size of the strength is small and difficult to read. Please increase the size of the strength commensurate with the proprietary and established names and add a space between the numerical strength “100” and the unit of measure “mg”.

3. The “Manufactured for/Manufactured by” information is inconsistent with the information in the Package Insert. We refer you to 21 CFR 201.1(h)(5) for further assistance.
5. DMETS recommends the “Rx Only” statement appear on the principal display panel. Revise accordingly.
6. According to 21 CFR 201.100 (b)(3) the route of administration statement “For Vaginal Use Only” must be included for drug products that are not administered orally. Additionally, we recommend using a different font color to improve the readability and increase the prominence of the unique route of administration.

C. CARTON LABELING (21 ——— tablets)

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1. See comments B1 through B2.
2. The route of administration statement blends in with the other labeling information. We recommend using a different font color and larger font size to make this statement clearer and more prominent to patients and healthcare providers. Please revise.
3. DMETS recommends replacing the statement “See enclosed patient package insert for direction for use” on the principal display panel with the statement “Usual dosage: See enclosed package inset. Use as directed by your physician.” which is currently located on the side panel. This will help to simplify the label. Revise accordingly.
4. The background color and font size of the distributor’s name, Ferring, provides added prominence. The distributor’s name may be misinterpreted as the proprietary name of the product. We recommend removing the background color and reducing the size of font used for the distributor’s name.

5. The statement "Each tablet contains 100 mg progesterone, USP" is redundant and clutters the main panel. Delete this statement from the main panel as it appears on the side panel of the carton labeling.
6. We recommend adding "Each box contains XX vaginal inserts and XX disposable applicators" to the package quantity statement to help clarify what is provided in the carton to the patient.
7. The carton labeling should clearly distinguish the difference in package quantity (21 tablets  
——— \. We recommend the use of boxing, bolding, or some other means of distinguishing each package quantity.

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**D. INSERT LABELING**

No comments at this time.

**E. PATIENT INSERT LABELING**

No comments at this time.

Appendix A. DMETS prescription study results for Endometrin

<u>Outpatient Rx</u>	<u>Voice</u>	<u>Inpatient Rx</u>
Endometrin	Endometrin	Endometrin
Endometrin	Endometren	Endometrin
Endometrin	Endometrin	Endometrin
Endometrin	Endometrin	Endometrin
Endometrian	Endometrin	Endometrin
Endometin	Endometrin	Endometrin
Endometrin	Endometrin	Endometrin
Endometrin	Enodmetrin	Endometrin
	Endometrin	Endometrin
	Endometrin	Endometrin
		Endometrin
		Endomethacin

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/s/  
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