PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-367 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: January 20,2003 (resubmission) Action Date: March 21, 2003

HFD 580 Trade and generic names/dosage form: Femring™ (estradiol acetate vaginal ring)

Applicant: Galen Holdings Therapeutic Class: hormone therapy

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Treatment of moderate to severe symptoms associated with the menopause

Is there a full waiver for this indication (check one)?

×Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
×Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

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cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960

301-594-7337

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Is there a full waiver for this indication (check one)?

×Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
×**Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Kassandra C. Sherrod
3/19/03 12:34:51 PM

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REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Application: NDA 21-367

Drug: [redacted]

Sponsor: Galen Holdings

Indications: Treatment of moderate to severe vasomotor symptoms associated with menopause, and

[redacted]

Galen requests a full waiver of the requirement for pediatric studies associated with the submission of this NDA. Thus, the waiver applies to all pediatric ages.

A disease-specific waiver is requested since the product is indicated for the treatment of symptoms of menopause in adults.

Per the provisions of the November 2000 draft Guidance to Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)), a justification for waiving pediatric studies is not included since a disease-specific waiver is being request.

NDA21-367
Estradiol acetate vaginal ring
(0.05 mg/day and 0.1 mg/day)
Galen Holdings

Group Leader Memo

See original clinical review for group leader's review and concurrence.

EXCLUSIVITY SUMMARY for NDA # 21-367 _____ SUPPL #

Trade Name Femring™_____ Generic Name estradiol acetate vaginal ring
Applicant Name Galen Holdings
HFD- 580
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_✔__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_✔__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /✔___/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_✔__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_✔__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /✔___/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_✓__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-472 Estring

NDA # 20-908 Vagifem

NDA # 20-323 Vivelle

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_✓__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✓__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✔__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_✔__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_✔__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_✔__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # IVR 1002

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__✔_/
Investigation #2	YES /___/	NO /_✔__/
Investigation #3	YES /___/	NO /_✔__/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_✔__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 , Study # IVR 1002

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /_✓__/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 N/A	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_✔__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-580/Division File
HFD-580/Sherrod
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T:Crescenzi

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Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Daniel A. Shames
3/20/03 04:26:14 PM

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NDA REGULATORY FILING REVIEW

NDA Number: 21-367
Requested Trade Name:
Generic Name and Strengths: (estradiol acetate vaginal ring) 0.05 mg/day and 0.10 mg/day)

Applicant: Galen Holdings

Date of Application: December 21, 2002
Date of Receipt: December 21, 2002
Date of Filing Meeting: February 7, 2002
Filing Date: February 19, 2002

Indication(s) requested: [redacted]

treatment of moderate-to-severe vasomotor symptoms

Type of Application: Full NDA __X__ Supplement _____
(b)(1) __X__ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S_2___ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)_____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain. NO

User Fee Status: Paid __X__ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__X__ NO_____
User Fee ID#___4234_____
Clinical data? YES __X__ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: ___October 20, 2002___

Action Goal Date (optional) __October 18, 2002___

- Does the submission contain an accurate comprehensive index? YES

- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES
  If no, for what ages and/or indications was a waiver and/or deferral requested: Waiver requested for pediatric population

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES

List referenced IND numbers: ———

End-of-Phase 2 Meeting? NO

Pre-NDA Meeting Date: November 7, 2000

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? YES

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment?
  If EA submitted, consulted to Nancy Sager (HFD-357)?
- Establishment Evaluation Request (EER) package submitted? NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

_____
Regulatory Project Manager, HFD-580

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/s/

Dornette Spell-LeSane
10/8/02 08:45:53 AM
CSO

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Filing Memorandum
Division of Reproductive and Urologic Drug Products

NDA 21-367/S-000

Trade Name:	[redacted]
Generic Name:	**Estradiol acetate vaginal ring**
Sponsor:	**Galen Limited** **Rockaway 80 Corporate Center** **100 enterprise Drive, Suite 280** **Rockaway, NJ 07866**
Classification:	**Estrogen**
Submission Date:	**December 19, 2001**
Date Received:	**December 21, 2001**
Indication:	**•Treatment of moderate-to-severe vasomotor symptoms associated with the menopause** [redacted]
Related Submission:	**IND** [redacted]
User Fee Goal Date:	**October 21, 2002**
Division Goal Date:	**October 14, 2002**
Filing Meeting Date:	**February 7, 2002**
Medical Reviewer:	**Theresa H. van der Vlugt, MD, M.P.H.**

Submission Resume

NDA 21-367 is an original new drug application. The estradiol acetate intravaginal ring is a soft, flexible polymer ring with a central core containing estradiol acetate intended for 3 months of intravaginal use for the treatment of vasomotor symptoms and vulvar and vaginal atrophy. Estradiol acetate is released from the IVR at rates equivalent to 0.05 mg of estradiol per day and 0.10 mg of estradiol per day.

The Sponsor currently markets Menoring® 50 in the UK (0.50 mg of estradiol/day), [redacted]

This submission includes the data from two Phase 3 clinical trial (Study IVR 1002 and Study HRT 8) performed to demonstrate the effectiveness of the estradiol acetate vaginal ring in the treatment of moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause and vulvar and vaginal atrophy (VVA).

Study IVR 1002, the primary efficacy and safety clinical trial, was a 13-week, double-blind, placebo-controlled, parallel group study conducted at 35 study sites in the US. Three hundred and thirty three (333) postmenopausal women, experiencing at least 7 MSVS per day (56 MSVS per week) were randomized to receive:

1) IVR delivering estradiol acetate equivalent to 0.05 mg of estradiol/day,
2) IVR delivering estradiol acetate equivalent to 0.10 mg of estradiol/day,
3) Placebo IVR.

Two hundred and seventy nine subjects completed the study. Significantly more subjects discontinued in the placebo group (29 of 108 subjects, 26.9%) than in the 0.50 mg of estradiol/day group (14 of 113 subjects, 12.4%) and the 0.10 mg of estradiol/day group (11 of 112 subjects, 9.8%). The most common reasons for discontinuation were adverse events (5.7%) and "other" reasons (5.4%). Intolerance to the ring or vaginal discomfort, and vaginal bleeding were some of the "other" reasons for discontinuance.

The second Phase 3 study submitted in the application (Study HRT 8), was a 24 week, double-blind, double-dummy, comparator-controlled, parallel group study conducted at 21 study sites in the UK. During the first 12 weeks of Study HRT 8, a total of 159 subjects experiencing at least 20 hot flushes/night sweats per week were randomized to receive:

1) IVR delivering estradiol acetate equivalent to 0.50 mg of estradiol/day plus an oral placebo tablet.
2) 1 mg oral estradiol tablet plus a placebo ring.

After 12 weeks, the dosage strengths could be increased for those women whose symptoms were not adequately controlled to: (1) IVR delivering estradiol acetate equivalent to 0.10 mg of estradiol/day plus a placebo tablet, or (2) 2 mg oral estradiol tablet plus a placebo ring. HRT 8 also included an additional 24-week open-label extension with active rings only.

Study HRT 8 does not comply with the Agency's HRT guidance for inclusion criteria and will be used as supportive for safety only. Study HRT 8 will not be considered a primary efficacy study.

Fileability of NDA 21-367/S-000

NDA 21-367/S-000 is fileable.

Review Issues

1) Incidence of epithelial redness, inflammation, granulation, ulceration and friability in all subjects.
2) Findings of petechiae, ecchymosis, erythema and peeling in the colposcopy examination in all treatment groups.
3) Subjects were considered to have vaginal atrophy at baseline if 20% or more of the sampled vaginal cells were parabasal cells.
4) Seven (7) of 35 participating clinical sites did not enroll subjects. However, study medication was randomized and shipped to sites in blocks of 6 sequential assignment numbers. We need to confirm that random treatment assignments were assured.

Request for Data

2/13/02 4p

1. The Sponsor is requested to provide a table showing the mean number of MSVS at baseline, week 4, week 8 and week 12, the mean change from baseline in the number of MSVS for week 4, week 8 and week 12, and the p value for week 4, week 8 and week 12 versus placebo for [redacted] 0.05 mg/day and [redacted] 0.10 mg/day using LOCF (ITT population) for Study IVR 1002.
2. The Sponsor is requested to provide a table showing the mean severity of hot flushes at baseline, week 4, week 8 and week 12, the mean change in severity at week 4, week 8 and week 12, and the p value for week 4, week 8 and week 12 versus placebo for [redacted] 0.05 mg/day and [redacted] .10 mg/day using LOCF (ITT population) for Study IVR 1002.
3. The Sponsor is requested to provide a table showing the mean percentage of parabasal, intermediate and superficial cells at baseline and week 12, and the mean change from baseline to week 12 for placebo, [redacted] 0.05 mg/day, and [redacted] 0.10 mg/day using the ITT population for Study IVR 1002.
4. The sponsor is requested to provide the SAS data sets created and the coding for the above requested tables.
5. The Sponsor is requested to provide the data set with ITT/LOCF values containing:
   - Subject ID
   - Protocol
   - Center ID
   - Dose/treatment
   - Date of study entry

for pivotal

- Date of study discontinuation
- Date on which the last visit is taken
- Primary reason for discontinuation
- Study completion? (yes/no)
- Baseline, week 4, week 8, week 12 MSVS
- Baseline, week 4, week 8, week 12 hot flush severity

Recommendations for a Division of Scientific Investigations Audit

[redacted]

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NDA: 21-367/S-000

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	X		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		Phase 3 Study HRT 8 will be used as supportive for safety only.
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X		
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-puts) previously requested by the Division	X		
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	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:			

Theresa H. van der Vlugt, M.D., M.P.H.
Medical Officer

Screening of New NDAs
Division of Biometrics II

NDA #: 20-367/S-000

Trade Name: [redacted] (estradiol acetate vaginal ring)

Sponsor: Galen Limited

Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause, and [redacted]

User Fee Goal Date: October 21, 2002

Division Goal Date: October 14, 2002

Date of Submission: December 19, 2001

Date of Filing Meeting: February 7, 2001

Medical Reviewer : Therasa van der Vlugt, M.D. (HFD-580)

Project Manager: Dornette Spell-LeSane (HFD-580)

Screened by: Moh-Jee Ng , M.S. (HFD-715)

Comments: Need to request datasets for this submission, this NDA is fileable

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CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (If present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient date listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies on diskettes and/or Electronic submitted	Request
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	NA

Brief Summary of Controlled Trials

Report # (Protocol #)	Study Design	Treatment Group	Sample Size	Duration of Treatment
RR 01101 (IVR 1002) Pivotal	Prospective, double-blind, randomized, placebo-controlled, parallel group, Multicenter study in postmenopausal women experiencing moderate to severe hot flushes	Estradiol acetate IVR delivering at a rate equivalent to : 0.05 m /day 0.1 mg/day Placebo IVR	333	13 weeks
RR 01401 (HRT 8) Supportive	Prospective, double-blind, randomized, comparator-controlled, parallel group, Multicenter study in postmenopausal women investigating effects on postmenopausal symptoms,	Estradiol IVR: 0.05 mg/day could be increased to 0.1 mg/day in Period 2 Oral estradiol: 1 mg/day could be increased to 2 mg/day in Period 2 Open label Treatment with IVR in Period 3	159	Period 1: 12 weeks Period 2: 12 weeks Period 3: 24 weeks

Moh-Jee Ng, M.S.
Mathematical Statistician

Concur: Mike Welch, Ph.D.

cc. NDA 21-367
HFD-580 / Division file
HFD-580 / TvanderVlugt, DSpell-LeSane, SSlaughter, DShames
HFD-715/ENevius, MWelch, CAnello, MNg,

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CONSULTATION RESPONSE

Division of Medication Errors and Technical Support

Office of Drug Safety

(DMETS; HFD-420)

DATE RECEIVED: August 27, 2002	**DUE DATE:** October 11, 2002	**ODS CONSULT #:** 01-0199-2

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dornette Spell-LeSane
Regulatory Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:**
[redacted], and Femring [redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.1 mg/day **NDA #** 21-367	Galen Limited

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names, [redacted] and "Femring", to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary names, [redacted] or [redacted] but has no objection to the use of the proprietary name "Femring". DMETS also recommends implementation of the labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

This name 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.

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Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3224 Fax (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 9, 2002

NDA NUMBER: 21-367

NAME OF DRUG: [redacted] and Femring [redacted]
(estradiol acetate vaginal ring)
0.05 mg/day and 0.1 mg/day

NDA SPONSOR: Galen Limited

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for an assessment of the proposed proprietary name, [redacted] and if necessary an assessment of the proposed proprietary names, [redacted], and Femring [redacted]. This proposed trademark was submitted with NDA 21-367. The sponsor initially submitted the name, [redacted] The Division of Reproductive and Urologic Drug Products did not accept [redacted], because the drug product (estradiol acetate) is not chemically the same as [redacted] (estradiol). Then the sponsor submitted the name [redacted] for consideration as the proprietary name. DMETS did not recommend the use of the name [redacted] due to the potential sound and look alike confusion with the proprietary name [redacted] The sponsor has now submitted three additional names [redacted] and Femring [redacted] to be considered as the proprietary name for this product. The container labels, carton and insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

[redacted] or Femring) contains the active ingredient estradiol acetate. The sponsor is seeking approval of this product for the treatment of moderate to severe vasomotor symptoms associated with menopause, and [redacted]

[redacted] The product is an off-white, soft, flexible polymer ring with a central core containing estradiol acetate. The product should be inserted into the vagina and left in place for 3 months. [redacted] is manufactured in two strengths of 0.05 mg/day and 0.1 mg/day. [redacted] should deliver 0.05 mg or 0.1 mg of estradiol per day for 3 months.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look alike to [redacted] and "Femring" 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 trademark electronic search system (TESS) was conducted[4]. The Saegis[5] 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 prescription analysis studies, 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.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names [redacted] and "Femring". Potential concerns regarding drug marketing and promotion related to the proposed names 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. The Expert Panel identified five proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).

[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

[3] The Drug Product Reference File [DPR], Established Evaluation System [EES], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

TABLE 1

Product Name	Generic name, Dosage form(s), and Strength(s)	Indication and usual adult dose	Other
[redacted]	Estradiol Acetate, Vaginal Ring, 0.05 mg/day and 0.1 mg/day	Treatment of moderate to severe vasomotor symptoms associated with menopause: Insert one vaginal ring into the vagina every 3 months	
Lotrel	Amlodipine/Benazepril HCL, Capsule, 2.5 mg/10 mg, 5 mg/10 mg and 5 mg/20 mg	Treatment of hypertension: Take one capsule orally daily.	L/A per DMETS
Lustra	Hydroquinone, Cream, 4%	Indicated to cause temporary bleaching of hyperpigmented skin conditions: Apply to the affected skin twice a day.	L/A per DMETS
Lodrane	Pseudoephedrine HCL and Brompheniramine Maleate, Tablet, 45 mg/6 mg Capsule, 60 mg/6 mg Liquid, 60 mg/4 mg per 5 mL	Treatment of upper respiratory symptoms: Tablet: Take 1 tablet every 12 hours. Capsule: Take 1 capsule every 12 hours. Liquid: Take 5 mL every 4 to 6 hours as needed. Up to 20 mL/day.	L/A and S/A per DMETS
Lactrase	Lactase Enzyme, Capsule, 250 mg	Indicated to digest lactose contained in milk for patients with lactose intolerance: Take one or two capsules with milk or dairy products.	L/A and S/A per DMETS
Estrace	Estradiol, Tablet, 0.5 mg, 1 mg, 1.5 mg, and 2 mg Vaginal Cream, 0.1 mg estradiol/gram	Treatment of moderate to severe vasomotor symptoms associated with menopause: Take one tablet orally daily.	L/A and S/A per DMETS

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in Table 2 (see page 5), along with the dosage forms available and usual dosage.

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TABLE 2

Product Name	Generic name, Dosage form(s) and Strength(s)	Indication and usual adult dose*	Other**
[redacted]	Estradiol Acetate Vaginal Ring, [redacted] mg/day and 0.1 mg/day	Treatment of moderate to severe vasomotor symptoms associated with menopause: Insert one vaginal ring into the vagina every 3 months.	
Vivelle	Estradiol, Transdermal System, 0.025 mg/24 hr, 0.0375 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr and 0.1 mg/24 hr	Treatment of moderate to severe vasomotor symptoms associated with menopause: Apply one patch to the skin twice weekly.	L/A per DMETS
Lunelle	Medroxyprogesterone Acetate/Estradiol Cypionate, Injection, 25 mg/5 mg per 0.5 ml	Indicated for the prevention of pregnancy: Inject intramuscularly 0.5 mL every 28 to 30 days.	L/A per DMETS
Kwell (Discontinued)	Gamma Benzene Hexachloride (Lindane), Lotion 1%, Shampoo 1%, And Cream 1%	Treatment of Pediculus capitis (head lice) and Pediculus pubis (crab lice) and their ova: Apply to affected area, allow medication to remain on skin for prescribed time based on condition and then wash. Reapplication may be required.	S/A per DMETS
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

3. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with "Femring". These products are listed in Table 3 (see below), along with the dosage forms available and usual dosage.

TABLE 3

Product Name	Generic name, Dosage form(s) and Strength(s)	Indication and usual adult dose*	Other**
Femring	Estradiol Acetate, Vaginal Ring, 0.05 mg/day and 0.1 mg/day	Treatment of moderate to severe vasomotor symptoms associated with menopause: Insert one vaginal ring into the vagina every 3 months.	
Femara	Letrozole, Tablets, 2.5 mg	Treatment of advanced breast cancer: Take one tablet orally daily.	S/A and L/A per DMETS
Nuvaring	Etonogestrel and Ethinyl Estradiol, Vaginal Ring, 0.12 mg/0.015 mg per day	Indicated for the prevention of pregnancy: Insert one vaginal ring into the vagina every 3 weeks, removed for 1 week, and then insert a new vaginal ring.	S/A per DMETS
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

4. DDMAC did not have any concerns with the promotional aspects of the names [redacted] or "Femring".

B. ADVERSE EVENT REPORTING SYSTEM SEARCH

A search of the FDA Adverse Event Reporting System (AERS) database was conducted for all postmarketing safety reports of medication errors involving proprietary names with the suffix "—". The search was conducted using the Meddra Preferred Term (PT), "Medication Error" and the proprietary names, Bravelle, Cryselle, Kwell, Lunelle, and Vivelle. Kwell is not spelled "—", but was added to the search due to the sound alike potential of the name.

The search did not identify any medication error reports of name confusion between medications ending in "—" or the proprietary name Kwell.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

Nine separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of "—" and Femring with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (nurses, pharmacists, and physicians) for "—", 106 health care professionals for "—" and 106 health care professionals for Femring. This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for "—" and Femring. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

"—" Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: [redacted]	*Outpatient:* "—" Use as directed Dispense 1
Inpatient: [redacted]	

——— Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: [redacted] 0.05mg/day #1 *Inpatient:* [redacted] 0.05	*Outpatient:* ———0.05 mg Use as directed Dispense 1

Femring Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Femring 0.1mg #1 *Inpatient:* Femring 0.1mg	*Outpatient:* Femring 0.1 mg As directed Number 1

2. Results

Results of the ——— exercises are summarized below:

Study	No. of participants	# of responses (%)	——— response	Other response
Written: Outpatient	39	27 (69%)	19 (70%)	8 (30%)
Inpatient	32	23 (72%)	22 (96%)	1 (4%)
Verbal: Outpatient	35	21 (60%)	17 (81%)	4 (19%)
Total:	106	71 (67%)	58 (82%)	13 (18%)

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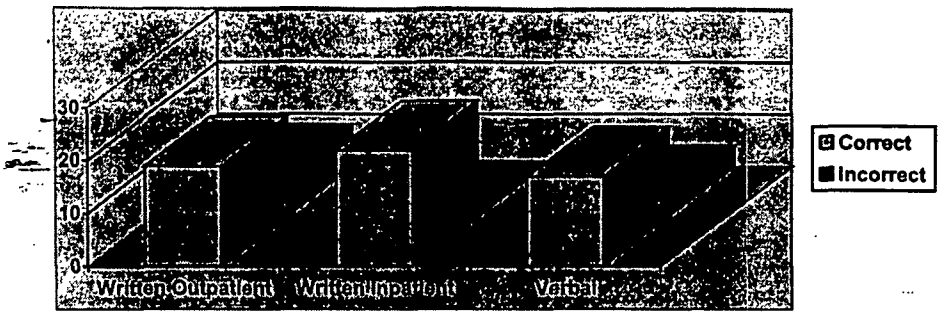


Among participants in the written outpatient prescription study, 19 of 27 respondents (70%) interpreted the name correctly. Incorrect interpretations included ——— (3), ——— (1), ——— 1), ——— (1), ——— (1) and ——— (1).

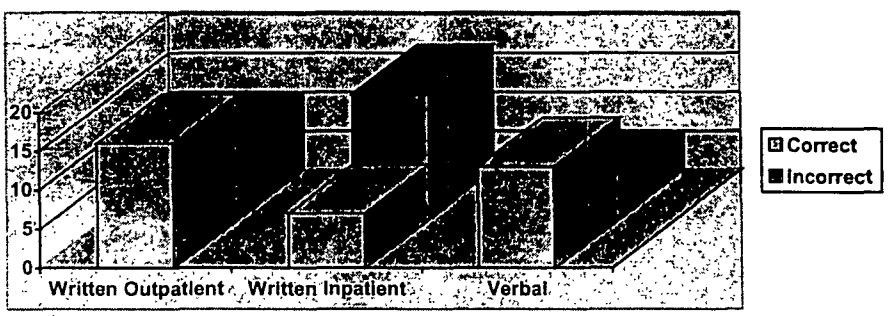
Among participants in the written inpatient prescription study, 22 of 23 respondents (96%) interpreted the name correctly. The only incorrect interpretation of the name was ——— (1).

Among participants in the verbal outpatient prescription study, 17 of 21 respondents (81%) interpreted the name correctly. The only incorrect interpretation of the name was ——— (4).

None of the incorrect interpretations of the name is a currently marketed drug product.

Results of the ——— exercises are summarized below:

Study	No. of participants	# of responses (%)	——— response	Other response
Written: Outpatient	32	26 (81%)	16 (62%)	10 (48%)
Inpatient	35	23 (66%)	7 (30%)	16 (70%)
Verbal: Outpatient	39	18 (46%)	13 (72%)	5 (28%)
Total:	106	67 (63%)	36 (54%)	31 (46%)



Among participants in the written outpatient prescription study, 16 of 26 respondents (62%) interpreted the name correctly. Incorrect interpretations included ——, (2), ——(6), ——(1), and —— (1).

Among participants in the written inpatient prescription study, 7 of 23 respondents (30%) interpreted the name correctly. Incorrect interpretations included —— (1), —— (1), ——(1), ——(2), ——(1), ——; (7), ——(1) and —— (2).

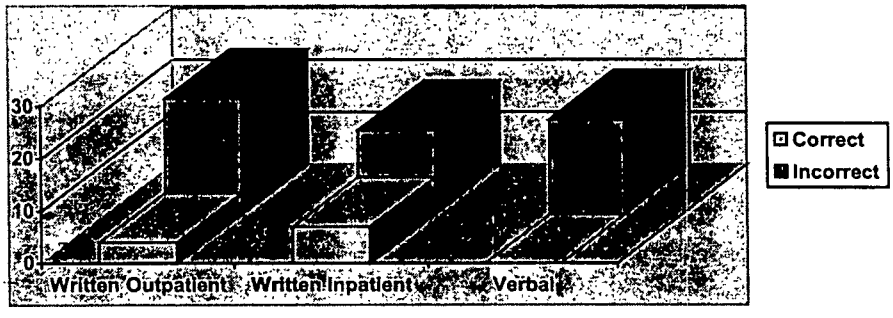
Among participants in the verbal outpatient prescription study, 13 of 18 respondents (72%) interpreted the name correctly. Incorrect interpretations included —— (3), ——(1), and —— (1).

None of the incorrect interpretations of the name is a currently marketed drug product. However, one participant in the written inpatient prescription study interpreted the name as —— The respondent indicated that if the interpretation was correct then the name would sound like Kwell.

Results of the Femring exercises are summarized below:

Study	No. of participants	# of responses (%)	"Femring" response	Other response
Written: Outpatient	32	26 (81%)	4 (15%)	22 (81%)
Inpatient	35	23 (66%)	7 (30%)	16 (70%)
Verbal: Outpatient	39	18 (46%)	0 (0%)	18 (100%)
Total:	106	67 (63%)	11 (16%)	56 (84%)

Among participants in the written outpatient prescription study, 4 of 26 respondents (15%) interpreted the name correctly. Incorrect interpretations included Derming (2), Denniz (1), Dermring (1), Feming (4), Fenning (2), Ferming (6), Geming (1), Jeming (1), Lemming (1), Teming (1), and Zemring (2).



Among participants in the written inpatient prescription study, 7 of 23 respondents (30%) interpreted the name correctly. Incorrect interpretations included Fenming (9), Fenning (4), Fenwing (2) and Ferming (1).

Among participants in the verbal outpatient prescription study, 0 of 18 respondents (0%) interpreted the name correctly. Incorrect interpretations included Famlin (1), Femarin (3), Femeran (1), Femerin (2), Femeron (1), Femrin (1), Fremaren (1),

Fumarin (1) Premarin (6) and Samarine (1). One respondent interpreted the name as Femarin, but indicated the name sounded like Premarin.

In the verbal outpatient prescription study, 6 respondents interpreted the name as Premarin a currently market medication in the U.S. marketplace. Another verbal outpatient prescription participant interpreted the name as Femarin, but indicated the name sounded like Premarin.

D. SAFETY EVALUATOR RISK ASSESSMENT

Proprietary Name Review

In reviewing the proprietary names "[redacted] and "Femring" the primary concerns raised were related to look alike and/or sound alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for confusion with "[redacted] were Lotrel, Lustra, Lodrane, Lactrase and Estrace, and with [redacted] were Vivelle, Lunelle and Kwell, and with "Femring" were Femara and Nuvaring.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that [redacted] could be confused with Lotrel, Lustra, Lodrane, Lactrase and Estrace, that [redacted] could be confused with Vivelle, Lunelle, and Kwell, or that Femring could be confused with Femara and Nuvaring. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed names, [redacted], and Femring.

However, one participant in the [redacted] written inpatient prescription study who interpreted the name as [redacted] commented if the interpretation was correct then the name would sound like Kwell. Also, six participants in the Femring verbal outpatient prescription study interpreted the name as Premarin a currently marketed medication in the U.S. marketplace. Another Femring verbal outpatient prescription participant interpreted the name as Femarin, but indicated the name sounded like Premarin. An evaluation for possible name confusion between Femring and Premarin can be found after the Nuvaring and Femring evaluation.

1. [redacted]

Lotrel is the proprietary name for a combination product containing amlodipine and benazepril hydrochloride. It is indicated for use in the treatment of hypertension. It is available as a capsule containing 2.5mg/10 mg, 5 mg/10 mg, or 5 mg/20 mg of amlodipine/benzapril hydrochloride. When scripted Lotrel and [redacted] can look similar. The [redacted]
Lotrel aids in differentiating the names, but if not scripted clearly, then the names can look similar. However, these medications have some important different characteristics. Lotrel and [redacted] have different strengths (2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg vs. 0.05 mg/day and 0.01 mg/day), package sizes (100 tablets vs. 1 vaginal ring), indication for use (hypertension vs. vasomotor symptoms associated with menopause), frequency of administration (daily vs. every 3 months), route of administration (orally vs. intravaginally), and dosage formulation (capsule vs. vaginal ring). Although these

names have the potential to look alike there are no other similar or overlapping characteristics. These other characteristics should decrease the potential risk for a medication error between these two drug products.

Lustra is the proprietary name for hydroquinone. Lustra is indicated for the temporary bleaching of hyperpigmented skin conditions (e.g., freckles, senile lentigines, chloasma and melasma; and other forms of melanin hyperpigmentation). Lustra is available as a 4% cream. The recommended dose is to apply the cream twice a day to the affected areas. Sunlight or UV light can cause repigmentation. It is recommended that sunblock agents be used to prevent this repigmentation. Lustra AF contains 4% hydroquinone cream with sunscreen protection. When scripted Lustra and ——— have the potential to look similar. The

[ ]

each name aids in differentiating the two names. Lustra and ——— have different product strengths (4% vs. 0.05 mg/day and 0.1 mg/day), package size (28.4 grams vs. 1 vaginal ring), indication for use (hyperpigmentation vs. vasomotor symptoms associated with menopause), dosage formulation (cream vs. vaginal ring), route of administration (topically vs. intravaginally) and frequency of administration (twice a day vs. every 3 months). These medications could be stored near each other if stocked in a general area containing ointments, creams and miscellaneous items. A Lustra prescription would not require the strength, since it is only available in one strength. However, a ——— prescription would require a strength, since it is available in two strengths. The strengths do not have any overlapping similarities with the expression of the digits (4 vs. 0.05 or 0.1) or units (% vs. mg/day). Although it is possible for the names to look alike, the risk of dispensing the wrong medication is low based on the differences between the medications. This includes no overlapping similarities in the directions for use or product strength.

Lodrane is the proprietary name for a decongestant and antihistamine combination product. Lodrane is available as an extended release tablet, liquid and capsule, and each formulation contains different amounts of pseudoephedrine HCl and brompheniramine maleate. This combination product is indicated to treat upper respiratory symptoms. Lodrane and ——— have the potential to look similar when scripted and sound similar when spoken. Both names

[ ]

[

Both names

]

Lodrane and ——— have different product strengths (45 mg/6 mg, 60 mg/4 mg per 5 mLand 60 mg/6 mg vs. 0.05 mg/day and 0.1 mg/day), package configurations (bottles vs. pouch), package size (100 tablets or capsules or 473 mL vs. 1 vaginal ring), indications for use (upper respiratory symptoms vs. vasomotor symptoms associated with menopause), frequency of administration (twice daily or every 4 to 6 hours vs. every 3 months), route of administration (orally vs. intravaginally) and dosage form (tablet, liquid and capsule vs. vaginal ring). A prescription for Lodrane would require the prescriber to indicate a product strength or dosage formulation, since each formulation is available in a different strength. Both the product strength or dosage formulation should differentiate Lodrane from ——— but

other characteristics such as directions for use, and quantity to be dispensed should also aid to differentiate the products. Although it is possible for the names to look and sound similar, the risk of dispensing the wrong medication is low based on the differences between the medications.

Lactrase is the proprietary name for a product containing 250 mg of standardized enzyme lactase. The product is indicated to digest lactose contained in milk for patients with lactose intolerance. Lactrase and ——— have the potential to look similar when scripted and sound similar when spoken. When scripted the feature that can aid in differentiating the two names is

[redacted]

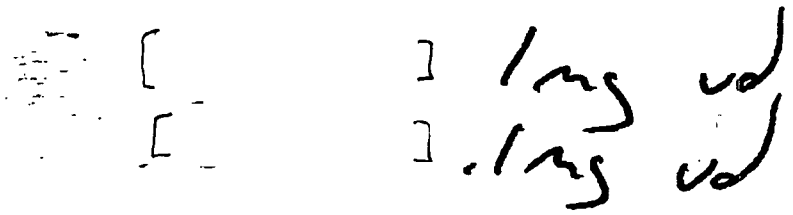
Lactrase and ——— have different product strengths (250 mg vs. 0.05 mg/day and 0.1 mg/day), package size (100 tablet bottles or 10 and 30 tablet blisterpacks vs. 1 vaginal ring), indications for use (lactose intolerance vs. vasomotor symptoms associated with menopause), frequency of administration (with milk or dairy products vs. every 3 months), route of administration (orally vs. intravaginally), dosage form (capsule vs. vaginal ring), and medication classification (over-the-counter vs. prescription). These two products should not be in close proximity with each other in a retail pharmacy, since Lactrase should be available for access by the general public in the over-the-counter medication section. The over-the-counter classification for Lactrase would also limit the number of prescriptions written or telephoned in to a pharmacy for this product. A prescription for ———would require the prescriber to indicate a product strength. The product strength should differentiate Lactrase from ———, but other characteristics such as directions for use, and quantity to be dispensed should also help to differentiate the products. Although it is possible for the names to look and sound similar, the risk of dispensing the wrong medication is low based on the differences between the medications.

Estrace is the proprietary name for estradiol. Estrace is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy, hypoestrogenism, advanced androgen dependent prostate carcinoma, and osteoporosis prevention. Estrace is available as 0.5 mg, 1 mg, 1.5 mg, and 2 mg tablets, and a 0.1 mg/g cream. Estrace and ——— have the potential to sound alike when spoken and look alike when scripted. Estrace and ——— can sound similar

[redacted]

Estrace and ——— can look alike [redacted] Since Estrace is available in two dosage formulations, tablets and vaginal cream, a separate comparison will be completed for each dosage formulation. Estrace tabs and ——— have different product strengths (0.5 mg, 1 mg, 1.5 mg, 2 mg vs. 0.05 mg/day and 0.01 mg/day), package configuration (bottle vs. pouch), dosage form (tablet vs. vaginal ring), route of administration (orally vs. intravaginally) and frequency of administration (daily vs. every 3 months). However, the characteristics listed above may not be enough to differentiate between the products. All prescriptions for Estrace tablets and ——— would require the product strength. Although the strengths are different, overlapping similarities of the numbers, 0.5 mg vs. 0.05 mg/day and 1 mg vs. 0.01 mg/day, can cause confusion. The directions for use could be spoken or written as, "ud or as

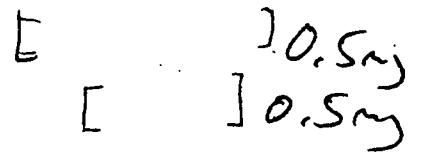
directed", and the quantity to be dispensed could be spoken or written as, "x month supply". Handwriting samples are included below for review and comparison.



Estrace vaginal cream and ——— have different product strengths (0.1 mg/gram vs. 0.05 mg/day and 0.01 mg/day), package configuration (tube vs. pouch), dosage formulation (cream vs. vaginal ring), and frequency of administration (daily vs. every 3 months). However, these two products also have some similar characteristics. These products can have the same route of administration (intravaginally) and indication for use (vasomotor symptoms associated with menopause). These medications could possibly be stored in the same locations within a pharmacy based on their route of administration (vaginal), classification of ingredients (estrogen products) or in a general ointment / cream area. Even though prescriptions for——— would require a product strength this may not absolutely distinguish ——— from Estrace cream. A prescription spoken or written for "——— 0.1 mg" could be interpreted as Estrace cream, since Estrace is available as a 0.1 mg estradiol/gram cream. Both medications could be used to treat the same patient population and prescribed by the same physicians. These two characteristics can create situations in which it may be harder for a nurse, pharmacist or patient to detect an error. If the prescription is misinterpreted, the patient may not realize that the medication may be wrong. Especially, since both medications are used to treat vasomotor symptoms associated with menopause and both are administered intravaginally. The immediate or short-term health consequences of a medication error involving these two medications should not result in a great potential for harm. Since both medications have a similar active ingredient and are approved to treat similar conditions. However, due to the possibility of the names looking and sounding similar and the many overlapping similarities of Estrace (tablets and vaginal cream) and ——— there is an increased potential for a medical error.

2. ———

Vivelle is the proprietary name for an estradiol transdermal system containing estradiol in a multipolymeric adhesive. Vivelle is indicated for a number of conditions, which includes the treatment of moderate to severe vasomotor symptoms associated with menopause. Vivelle is available in five different strengths manufactured to deliver estradiol at a continuous rate. The recommended dose is to apply one patch to the skin twice weekly. When scripted Vivelle and ——— have the potential to look similar. When scripted ——— Also both names ——— When scripted ——— A handwriting sample is included below for review and comparison.



Vivelle and ——— have a different package size (calendar pack containing 8 systems vs. 1 vaginal ring), dosage formulation (patch vs. vaginal ring), route of administration (topically vs. intravaginally) and frequency of administration (twice weekly vs. every 3 months). However, these two medications share overlapping strengths (0.05 mg/24 hour or day and 0.1 mg/24 hour or day) and the indication for use (vasomotor symptoms associated with menopause). Although these medications have different active ingredients, estradiol acetate vs. estradiol, the expression of strength indicates the amount of estradiol delivered to the patient per day. Therefore, if the products were used correctly and the patient did not have any contraindications to either the delivery system or inactive ingredients in either product then the potential for harm should be low. However, due to the possibility of the names looking similar along with the overlapping strengths of the medications there is an increased risk for a medication error.

Lunelle is the proprietary name for an injection containing 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate per 0.5 mL. The combination medication is available in 0.5 mL single dose vials. Lunelle is indicated for contraception in the prevention of pregnancy. The recommended dose is 0.5 mL administered by IM injection within the first 5 days of the onset of a normal menstrual period. Lunelle and ——— have the potential to sound alike when spoken and look alike when scripted. Lunelle and ——— can sound similar

Lunelle and ——— have the potential to look similar

[redacted]

Lunelle and ——— have a different package size (1 single dose vial vs. 1 vaginal ring), dosage formulation (injection vs. vaginal ring), route of administration (intramuscularly vs. intravaginally), indication for use (contraception vs. vasomotor symptoms associated with menopause) and frequency of administration (every month vs. every 3 months). However, these two medications share overlapping digits in the expression of the dose (0.5 mL vs. 0.05 mg). Therefore, if the directions are only written as "ud or as directed", then the dose of 0.5 mL could be misinterpreted as 0.05 mg. However, the risk of administering the wrong medication on an outpatient basis should be low since if a patient was dispensed Lunelle the patient would need a prescription for intramuscular syringes or be informed to return to their physician. Also, if the physician instructed a patient the medication was an injectable and the patient was dispensed ———, then the patient should suspect a dispensing error. The risk of a patient being administered the wrong medication may be greater in a hospital or long term care facility were the patient may not be cognizant of all medications being administered. Due to the possibility that the names sound similar along with the overlapping digits in the expression of the strengths there is an increased risk for a medication error.

Kwell is the proprietary name for lindane or gamma benzene hexachloride. The proprietary name Kwell is no longer available in the U.S. marketplace, but the name is widely recognized by healthcare professionals. There are numerous manufacturers of lindane. Lindane is indicated for the treatment of Pediculus capitis (head lice) and Pediculus pubis (crab lice) and their ova. The product is also indicated for Sarcoptes scabiei (scabies). Lindane is available as a lotion and shampoo. When spoken Kwell

and [redacted] have the potential to sound alike. Although Kwell [redacted] . Kwell and [redacted] have a different package size (30 mL, 60 mL or 480 mL vs. 1 vaginal ring), dosage formulation (lotion or shampoo vs. vaginal ring), route of administration (topical vs. intravaginally), indication for use (lice and scabies vs. vasomotor symptoms associated with menopause) and frequency of administration (once with a possible reapplication vs. every 3 months). Although it is possible for the names to sound similar, the risk of dispensing the wrong medication is low based on the many differences between the medications.

3. FEMRING

Femara is the proprietary name for letrozole. The medication is only available in a 2.5 mg tablet. Femara is indicated as a first line treatment in postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. The recommended dose is one 2.5 mg tablet daily, without regards to meals. Femara and Femring have the potential to sound alike when spoken and look alike when scripted. Femara and Femring can sound similar since both names begin with exactly the same first syllable, "Fem". When scripted Femara and Femring have the potential to look similar since both names begin with the same first syllable and the names appear to have a similar length. Femara contains 6 letters and Femring contains 7 letters. Femara and Femring have different product strengths (2.5 mg vs. 0.05 mg/day and 0.1 mg/day), package size (30 tablets vs. 1 vaginal ring), dosage formulation (tablets vs. vaginal ring), route of administration (orally vs. intravaginally), indication for use (breast cancer, advanced vs. vasomotor symptoms associated with menopause) and frequency of administration (daily vs. every 3 months). Although it is possible for the names to sound and look similar the risk of dispensing the wrong medication is low based on the differences between the medications.

Nuvaring is the proprietary name for a combination product containing etonogestrel and ethinyl estradiol. The medication is available in a vaginal ring. Nuvaring is indicated for the prevention of pregnancy. The recommended dose is to insert one ring intravaginally for 3 weeks and then remove the ring for 1 week before inserting a new ring. When spoken Nuvaring and Femring have the potential to sound alike since both names end with exactly the same last syllable, "ring". Nuvaring and Femring have different product strengths (0.12 mg/0.015 mg per day vs. 0.05 mg/day and 0.1 mg/day), indication for use (prevention of pregnancy vs. vasomotor symptoms associated with menopause) and frequency of administration (every month vs. every 3 months). An oral or written prescription for Femring would require the product strength. Although there are some overlapping digits the expression of the strengths should aid in differentiating the products. Although the route of administration is the same, the duration of treatment is different (3 weeks intravaginally, 1 week removed, then repeat vs. continuous for 3 months). Although it is possible for the names to sound similar the risk of dispensing the wrong medication is low based on the differences between the medications.

Results from the verbal outpatient prescription study indicated the name Femring can sound like Premarin. Six of eighteen respondents interpreted the name as Premarin, and another respondent commented the name sounded like Premarin. Premarin is the proprietary name for conjugated estrogens. The medication is available as a tablet, injection and vaginal cream. Premarin cream and Femring vaginal ring share the same route of administration (intravaginally), and the Premarin tablets/cream and Femring share

overlapping indications for use. However, Premarin and Femring have different product strengths (0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg tablets; 25 mg/vial injection; 0.625 mg/g cream vs. 0.05 mg/day and 0.01 mg/day), package configuration (bottle, vial or tube vs. pouch), and dosage formulation (tablet, parenteral, or cream vs. vaginal ring). Prescriptions for Premarin and Femring would require a product strength since the medications are available in multiple strengths. Premarin cream and Femring share the same route of administration, however the directions for these medications are different. A verbal prescription for Premarin cream could be written with the directions "as directed" and dispense "1". However, the prescriber would need to indicate the dosage formulation (cream) or product strength (0.625 mg/g). Either one of these two characteristics would differentiate Premarin cream from the other Premarin dosage formulations and from Femring. Although it is possible for the names to sound alike, the risk of dispensing the wrong medication is low based on the differences between the medications.

III. COMMENTS TO THE SPONSOR:

1. The Proprietary Name Review

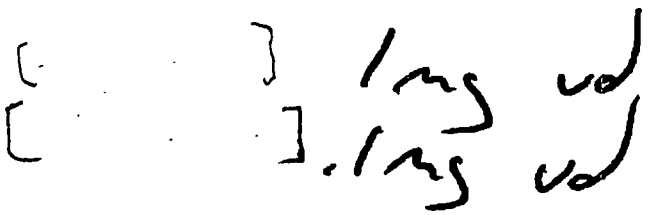
The Division of Medication Errors and Technical Support does not recommend the use of the proprietary names ———. The primary concern for ——— was related to the proprietary name Estrace and for——— was related to the proprietary names Vivelle and Lunelle that already exist in the U.S. marketplace. The Division of Medication Errors and Technical Support has no objections to the use of the proprietary name Femring.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that ——— could be confused with Lotrel, Lustra, Lodrane, Lactrase and Estrace, that ——— could be confused with Vivelle, Lunelle, and Kwell or that Femring could be confused with Femara and Nuvaring. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed names, ——— and Femring. However, one participant in the ——— written inpatient prescription study who interpreted the name as ——— commented if the interpretation was correct then the name would sound like Kwell. Also, six participants in the Femring verbal outpatient prescription study interpreted the name as Premarin a currently marketed medication in the U.S. marketplace. Another Femring verbal outpatient prescription participant interpreted the name as Femarin, but indicated the name sounded like Premarin.

Estrace is the proprietary name for estradiol. Estrace is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy, hypoestrogenism, advanced androgen dependent prostate carcinoma, and osteoporosis prevention. Estrace is available as 0.5 mg, 1 mg, 1.5 mg, and 2 mg tablets, and a 0.1 mg/g cream. Estrace and ——— have the potential to sound alike when spoken and look alike when scripted. Estrace and ———can sound similar

[Estrace and ——— can look alike ———]. Since Estrace is available in two dosage formulations, tablets and vaginal cream, a separate comparison will be completed for each dosage formulation. Estrace tabs and ———have different product strengths (0.5 mg, 1 mg,

1.5 mg, 2 mg vs. 0.05 mg/day and 0.01 mg/day), package configuration (bottle vs. pouch), dosage form (tablet vs. vaginal ring), route of administration (orally vs. intravaginally) and frequency of administration (daily vs. every 3 months). However, the characteristics listed above may not be enough to differentiate between the products. All prescriptions for Estrace tablets and ——— would require the product strength. Although the strengths are different, overlapping similarities of the numbers, 0.5 mg vs. 0.05 mg/day and 1 mg vs. 0.01 mg/day, can cause confusion. The directions for use could be spoken or written as, "ud or as directed", and the quantity to be dispensed could be spoken or written as, "x month supply". Handwriting samples are included below for review and comparison.



Estrace vaginal cream and ——— have different product strengths (0.1 mg/gram vs. 0.05 mg/day and 0.01 mg/day), package configuration (tube vs. pouch), dosage formulation (cream vs. vaginal ring), and frequency of administration (daily vs. every 3 months). However, these two products also have some similar characteristics. These products can have the same route of administration (intravaginally) and indication for use (vasomotor symptoms associated with menopause). These medications could possibly be stored in the same locations within a pharmacy based on their route of administration (vaginal), classification of ingredients (estrogen products) or in a general ointment/cream area. Even though prescriptions for ——— would require a product strength this may not absolutely distinguish ——— from Estrace cream. A prescription spoken or written for ——— 0.1 mg" could be interpreted as Estrace cream, since Estrace is available as a 0.1 mg estradiol/gram cream. Both medications could be used to treat the same patient population and prescribed by the same physicians. These two characteristics can create situations in which it may be harder for a nurse, pharmacist or patient to detect an error. If the prescription is misinterpreted, the patient may not realize that the medication may be wrong. Especially, since both medications are used to treat vasomotor symptoms associated with menopause and both are administered intravaginally. The immediate or short-term health consequences of a medication error involving these two medications should not result in a great potential for harm. Since both medications have a similar active ingredient and are approved to treat similar conditions. However, due to the possibility of the names looking and sounding similar and the many overlapping similarities of Estrace (tablets and vaginal cream) and ———there is an increased potential for a medical error.

Vivelle is the proprietary name for an estradiol transdermal system containing estradiol in a multipolymeric adhesive. Vivelle is indicated for a number of conditions, which includes the treatment of moderate to severe vasomotor symptoms associated with menopause. Vivelle is available in five different strengths manufactured to deliver estradiol at a continuous rate. The recommended dose is to apply one patch to the skin twice weekly. When scripted Vivelle and ——— have the potential to look similar. When scripted ——— Also both names ——— When scripted ——— A handwriting sample is included below for review and comparison.

[ ] 0.5mg
[ ] 0.5mg

Vivelle and [redacted] have a different package size (calendar pack containing 8 systems vs. 1 vaginal ring), dosage formulation (patch vs. vaginal ring), route of administration (topically vs. intravaginally) and frequency of administration (twice weekly vs. every 3 months). However, these two medications share overlapping strengths (0.05 mg/24 hour or day and 0.1 mg/24 hour or day) and the indication for use (vasomotor symptoms associated with menopause). Although these medications have different active ingredients, estradiol acetate vs. estradiol, the expression of strength indicates the amount of estradiol delivered to the patient per day. Therefore, if the products were used correctly and the patient did not have any contraindications to either the delivery system or inactive ingredients in either product then the potential for harm should be low. However, due to the possibility of the names looking similar along with the overlapping strengths of the medications there is an increased risk for a medication error.

Lunelle is the proprietary name for an injection containing 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate per 0.5 mL. The combination medication is available in 0.5 mL single dose vials. Lunelle is indicated for contraception in the prevention of pregnancy. The recommended dose is 0.5 mL administered by IM injection within the first 5 days of the onset of a normal menstrual period. Lunelle and [redacted] have the potential to sound alike when spoken and look alike when scripted. Lunelle and [redacted] can sound similar [redacted]

Lunelle and [redacted] have the potential to look similar

[redacted]

. Lunelle and [redacted] have a different package size (1 single dose vial vs. 1 vaginal ring), dosage formulation (injection vs. vaginal ring), route of administration (intramuscularly vs. intravaginally), indication for use (contraception vs. vasomotor symptoms associated with menopause) and frequency of administration (every month vs. every 3 months). However, these two medications share overlapping digits in the expression of the dose (0.5 mL vs. 0.05 mg). Therefore, if the directions are only written as "ud or as directed", then the dose of 0.5 mL could be misinterpreted as 0.05 mg. However, the risk of administering the wrong medication on an outpatient basis should be low since if a patient was dispensed Lunelle the patient would need a prescription for intramuscular syringes or be informed to return to their physician. Also, if the physician instructed a patient the medication was an injectable and the patient was dispensed [redacted] then the patient should suspect a dispensing error. The risk of a patient being administered the wrong medication may be greater in a hospital or long term care facility were the patient may not be cognizant of all medications being administered. Due to the possibility that the names sound similar along with the overlapping digits in the expression of the strengths there is an increased risk for a medication error.

2. Labeling, Packaging and Safety Related Issues

DMETS has reviewed the container label, carton labeling, and package insert labeling in an

attempt to focus on safety issues to prevent possible medication errors. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety.

Some of the areas of possible improvement listed below were noted in a previous DMETS consult (consult 01-0199-1). The new container label does present the entire proprietary name in one color as recommended in the previous consult. However, the proposed label does not demonstrate the following recommended revisions.

A. Container Label (pouch)

1. Increase the prominence of the product strength (0.05 mg/day and 0.1 mg/day).

2. Remove the [redacted] from the presentation of the [redacted] product strength to read "0.1 mg/day".

3. The colors used to differentiate the strengths are similar ([redacted]). DMETS suggest the use of two colors with more contrast.

4. Change the inactive ingredient statement to include the word "silicone" in association with "cured elastomer" to read "cured silicone elastomer".

5. Include a "Usual Dosage" statement on the labeling.

6. A statement should be included as to whether or not the pouch is child resistant. If it is not child resistant, we encourage the inclusion of a statement that if dispensed outpatient, it should be in a child resistant container. For example:

   This pouch package is not child resistant. If dispensed for outpatient use, a child resistant container should be utilized. [Note: The second sentence is optional.]

B. Carton Labeling

1. See comments A1 – A2.

2. The principal display panel on the 0.1 mg/day vaginal ring carton displays the product strength in black type surrounded by a [redacted] background. Please present the product strength in a more contrasting color.

3. Increase the prominence of the "mg/day", where the "mg/day" information is presented in black type.

4. Decrease the prominence of the pictures on the principal display panels to be no larger than 1/3 of the label.

5. The physician sample carton labeling contains the phrase "Physician's Sample – Not For Sale". The phrase is located between the established name and product strength. Relocate the phrase so the established name and product strength are presented in sequence.

C. Package Insert Labeling

1. The "Precautions: B. [redacted] section reads [redacted] Revise to read

2. The first sentence in the "Dosage and Administration" section reads ' [redacted] Please change the word ' [redacted] to read [redacted]

3. The "How Supplied" section does not state if the product is in a child-resistant package." Include the appropriate information refer to comment A6.

4. In the Description section of the INFORMATION FOR PATIENTS it reads [redacted] is made of cured elastomer..." Please include the word "silicone" in association with "cured elastomer" to read "cured silicone elastomer".

IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary names, [redacted] ', but has no objection to the use of the proprietary name, "Femring".

2. DMETS recommends the labeling revisions outlined in Section III to encourage the safest possible use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

APPEARS THIS WAY
ON ORIGINAL

Denise Toyer, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Scott Dallas
10/16/02 02:08:18 PM
PHARMACIST

Carol Holquist
10/18/02 01:01:14 PM
PHARMACIST

Jerry Phillips
10/21/02 09:30:52 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: August 23, 2001	**DUE DATE:** January 31, 2002	**ODS CONSULT #:** 01-0199

TO: Daniel Shames, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dornette Spell-LeSane
Project Manager
HFD-580

PRODUCT NAME: [redacted] (estradiol acetate vaginal ring) 0.05 mg/day and 0.1 mg/day **IND #:** [redacted]	**IND SPONSOR:** Warner Chilcott Laboratories

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the modifier "[redacted]" in conjunction with the proprietary name, [redacted] We recommend that the sponsor label the proposed product as [redacted]

APPEARS THIS WAY
ON ORIGINAL

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Food and Drug Administration

The Division of Medication Errors and Technical Support

Office of Drug Safety (ODS)

HFD-400; Parklawn Building Room 15B-32

Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **January 22, 2002**

IND NUMBER: ———

NAME OF DRUG: ———
(estradiol acetate vaginal ring)
0.05 mg/day and 0.1 mg/day

IND SPONSOR: **Warner Chilcott Laboratories**

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the proprietary name, ———

The sponsor, Warner Chilcott, currently markets several Estrace products, with the following strengths and active ingredient:

Estrace (estradiol vaginal cream, USP, 0.01%)
Estrace (estradiol tablets, USP, 0.5 mg, 1 mg, and 2 mg)

PRODUCT INFORMATION

——— is an ——— will be available as an estradiol acetate vaginal ring. The vaginal ring is a reservoir system that contains a central core, which is surrounded by ——— ——— is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause and ——— One ——— is to be inserted into the upper third of the vagina every 3 months. ——— 0.05 mg/day contains 12.4 mg of estradiol acetate that releases estradiol at a rate equivalent to 50 mcg per day for 3 months. ——— 0.1 mg/day contains 24.8 mg of estradiol acetate that releases estradiol at a rate equivalent to 100 mcg per day for 3 months.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because [redacted] An Expert Panel discussion was conducted to address concerns with the use of the modifier [redacted]. In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any current confusion with the use of the proprietary name '[redacted]

A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS's Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising 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. The DMETS Expert Panel concluded that simply labeling the product " [redacted] would be more appropriate than the addition of ' [redacted] to the proprietary name. The labeling statement, [redacted] ' clearly distinguishing it from [redacted]

2. DDMAC did not have any concerns about the names with regard to promotional claims.

B. AERS and DQRS DATABASE SEARCHES

We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with [redacted] The Meddra Preferred Term (PT), "Medication Error," and the drug name, ' [redacted] were used to perform the search.

This search strategy retrieved zero medication error reports of name confusion involving [redacted]

C. SAFETY EVALUATOR RISK ASSESSMENT

[redacted], but the Agency has not received any medication error reports of name confusion involving [redacted] Therefore, we have no concerns with the root name, [redacted]

The proposed product, [redacted]. However, the proposed product, [redacted] will be available as an estradiol vaginal ring. We recognize the need to differentiate the currently marketed [redacted] products from this new product, [redacted] However, the modifier, [redacted], which is interpreted as ' [redacted], is misleading. Although the suffix, ' [redacted], may have been intended to represent [redacted] ' this abbreviation represents that of a standard medical abbreviation meaning [redacted] ' [redacted] ' and others. The Agency has always considered use of coined abbreviations in conjunctions with proprietary names objectionable, since they can and have been misinterpreted. We acknowledge that there is one approved proprietary name containing the

modifier '[redacted] is available as 500 mcg/mL injection for the [redacted] However, the name, [redacted], was approved prior to formation of the Center's current review process of proprietary names.

In conclusion, the DMETS Expert Panel concluded that simply labeling the product "[redacted] would be more appropriate than the addition of "[redacted]" to the proprietary name. The labeling statement, [redacted]' clearly distinguishing it from [redacted] In addition, the term, [redacted] is more informative and less ambiguous than the "[redacted]' for prescribers and dispensing pharmacists.

D. COMMENTS TO BE PROVIDED TO THE SPONSOR

DMETS does not recommend the use of the modifier '[redacted]' in conjunction with the proprietary name, [redacted] We recommend that the sponsor label the proposed product as [redacted]

The proposed product, [redacted] However, the proposed product, [redacted] will be available as an estradiol vaginal ring. We recognize the need to differentiate the currently marketed [redacted] products from this new product, [redacted] However, the modifier, [redacted] which is interpreted as [redacted], is misleading. Although the suffix, '[redacted]', may have been intended to represent [redacted]' this abbreviation represents that of a standard medical abbreviation meaning '[redacted]" and others. The Agency has always considered use of coined abbreviations in conjunctions with proprietary names objectionable, since they can and have been misinterpreted. We acknowledge that there is one approved proprietary name containing the modifier '[redacted] is available as 500 mcg/mL injection for the [redacted] However, the name, '[redacted], was approved prior to formation of the Center's current review process of proprietary names.

In conclusion, the DMETS Expert Panel concluded that simply labeling the product '[redacted] would be more appropriate than the addition of '[redacted]" to the proprietary name. The labeling statement, [redacted] " clearly distinguishing it from [redacted] In addition, the term, ' [redacted] " is more informative and less ambiguous than the "[redacted]" for prescribers and dispensing pharmacists.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Not provided for review.

IV. RECOMMENDATIONS

DMETS does not recommend the use of the modifier "[redacted] in conjunction with the proprietary name, [redacted] We recommend that the sponsor label the proposed product as "[redacted]

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OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Drug Safety (ODS)

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/s/

Hye-Joo Kim
1/28/02 11:54:44 AM
PHARMACIST

Carol Holquist
1/28/02 01:22:10 PM
PHARMACIST

Jerry Phillips
1/29/02 10:14:44 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

3.4 FOREIGN MARKETING HISTORY

[redacted] 0.05 mg/day is registered for marketing in the United Kingdom under the proprietary name Menoring® 50. The Menoring 50 Marketing Authorization application was submitted on February 12, 1999. Menoring 50 was registered on April 3, 2001 and has been in the market since June 2001; its marketing authorization number is PL 00440/0117. Menoring 50 has not been withdrawn from any market due to safety concerns.

[redacted]