

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-102**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**ITEM 13**  
**PATENT AND MARKET EXCLUSIVITY INFORMATION**

This section of the NDA provides patent information required under Section 21 U.S.C. 355(b)(1) and documents the market exclusivity period applicable to FemHRT.

**13.1. Patent Information**

NDA Number: 21-065

Applicant: Parke-Davis Pharmaceutical Research  
Division of Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, MI 48106

Active Ingredient: HRT is a 1:1 ratio of ethinyl estradiol and norethindrone acetate. The empirical formula of HRT is  $C_{20}H_{24}O_2$  (ethinyl estradiol) and  $C_{22}H_{28}O_3$  (norethindrone acetate) and the molecular weight is 636.87.

Medical Use: HRT is continuous orally administered combination of norethindrone acetate/ethinyl estradiol for prevention of osteoporosis and treatment of hypoestrogenic states, especially those associated with the perimenopause, menopause, and following oophorectomy.

Strength:   
1 mg norethindrone acetate/5 µg ethinyl estradiol

Dosage Form: Tablet

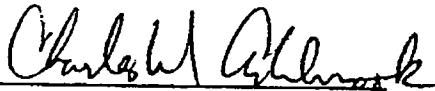
Trade Name: FemHRT™

Generic Name: norethindrone acetate/ethinyl estradiol

Patent Statement: One patent covers HRT

US Patent Number: 5,208,225  
Expiration Date: May 4, 2010  
Patent Type: Method of use  
Assignee: Warner-Lambert Company

The undersigned declares that Patent No. 5,208,225 covers the method of use of FemHRT which is the subject of this application which approval is sought.



Charles W. Ashbrook  
Assistant General Counsel  
Pharmaceutical Patents  
Warner-Lambert Company

**ITEM 13.2.**

**Request and Justification for 3-Year Marketing Exclusivity**

Warner-Lambert Company requests 3 years of market exclusivity for FemHRT™ (hormone replacement therapy, hereafter referred to as HRT). Warner-Lambert Company certifies that the active ingredients in FemHRT™, norethindrone acetate and ethinyl estradiol, meet the criteria for the exclusivity period specified in 21 USC §355(j)(4)(D)(iii) and 355(c)(3)(D)(iii), specifically:

1. No drug product containing the same strengths of active ingredients, norethindrone acetate and ethinyl estradiol, in combination, have been previously approved for which approval is sought in this application. The combination of active ingredients, norethindrone acetate and ethinyl estradiol, have been previously approved.
- 2.a. Four new clinical investigations, other than bioavailability and bioequivalence studies, were submitted to support this application. Warner-Lambert Company certifies that to the best of applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.
- b. The new clinical investigations can be found in Item 8 of the application, NDA No. 21-065, filed concurrently herewith.
- 3.a. Item 8 of the application, NDA 21-065, filed concurrently herewith, list all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to support this application.
- b. Warner-Lambert Company certifies that applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports is complete and accurate.
- c. Warner-Lambert Company certifies that, in applicant's opinion, the present application could not have been approved without the new clinical investigations. The published studies noted in 3.a above are not sufficient to support the approval of the application.

4. Warner-Lambert Company is the sponsor named in Form FDA 1571 for IND:  under which the clinical investigation identified in 2 above was performed.

APPEARS THIS WAY  
ON ORIGINAL

# Exclusivity Checklist

|                                                                                                                                                                                                                                                                                                                 |     |                                        |                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------------|-------------------------------------|
| NDA: 21-102 (osteoporosis prevention indication unbundled from NDA 21-065)                                                                                                                                                                                                                                      |     |                                        |                                     |
| Trade Name: <i>Levopt<sup>TM</sup></i>                                                                                                                                                                                                                                                                          |     |                                        |                                     |
| Generic Name: <i>1mg NORETHINDRONE ACETATE / 5mcg ETHINYL ESTRADIOL tablets</i>                                                                                                                                                                                                                                 |     |                                        |                                     |
| Applicant Name: <i>PARKE DAVIS PHARMACEUTICAL RESEARCH</i>                                                                                                                                                                                                                                                      |     |                                        |                                     |
| Division: <i>510 DMEDP</i>                                                                                                                                                                                                                                                                                      |     |                                        |                                     |
| Project Manager: <i>ENID GALLIERS</i>                                                                                                                                                                                                                                                                           |     |                                        |                                     |
| Approval Date: <i>15-OCT-1999</i>                                                                                                                                                                                                                                                                               |     |                                        |                                     |
| <b>PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?</b>                                                                                                                                                                                                                                                          |     |                                        |                                     |
| 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 | <input checked="" type="checkbox"/> No |                                     |
| b. Is it an effectiveness supplement?                                                                                                                                                                                                                                                                           | Yes | No                                     | <input checked="" type="checkbox"/> |
| c. If yes, what type? (SE1, SE2, etc.)                                                                                                                                                                                                                                                                          |     |                                        |                                     |
| 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 | <input checked="" type="checkbox"/> 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. |     |                                        |                                     |
| Explanation:                                                                                                                                                                                                                                                                                                    |     |                                        |                                     |
| 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:                                                                                                                                     |     |                                        |                                     |
| Explanation:                                                                                                                                                                                                                                                                                                    |     |                                        |                                     |
| d. Did the applicant request exclusivity?                                                                                                                                                                                                                                                                       | Yes | <input checked="" type="checkbox"/> No |                                     |
| If the answer to (d) is "yes," how many years of exclusivity did the applicant request?                                                                                                                                                                                                                         | 3   |                                        |                                     |
| <b>IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.</b>                                                                                                                                                                                                            |     |                                        |                                     |
| 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?                                                                                                                                      | Yes | No                                     | <input checked="" type="checkbox"/> |
| If yes, NDA #                                                                                                                                                                                                                                                                                                   |     |                                        |                                     |
| Drug Name:                                                                                                                                                                                                                                                                                                      |     |                                        |                                     |
| IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE                                                                                                                                                                                                                                              |     |                                        |                                     |

**BLOCKS.**

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 (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. Yes ☐ No ☒

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).

|              |  |
|--------------|--|
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |

2. Combination product. Yes ☐ ☒ No ☐

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).

|              |  |
|--------------|--|
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |
| Drug Product |  |
| NDA #        |  |

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

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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.**

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 BLOCKS.**

Basis for conclusion:

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 | <input checked="" type="checkbox"/> |
| 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 #:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  | 376-359 |     |    |                                     |
| 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 | <input checked="" type="checkbox"/> |
| Investigation #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | N/A     | Yes | No |                                     |
| Investigation #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | N/A     | 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:                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |         |     |    |                                     |
| Investigation #1 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| Investigation #2 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| Investigation #3 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| 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 | <input checked="" type="checkbox"/> |
| Investigation #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | N/A     | Yes | No |                                     |
| Investigation #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | N/A     | Yes | No |                                     |
| If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |         |     |    |                                     |
| Investigation #1 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| Investigation #2 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| Investigation #3 -- NDA Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |         |     |    |                                     |
| 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | 376-359 |     |    |                                     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |     |                                     |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----|-------------------------------------|----|
| Investigation #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | N/A     |     |                                     |    |
| Investigation #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | N/A     |     |                                     |    |
| <p>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.</p> |         |     |                                     |    |
| <p>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?</p>                                                                                                                                                                                                                                                                                                                                                                                      |         |     |                                     |    |
| Investigation #1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 376-359 | Yes | <input checked="" type="checkbox"/> | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| Investigation #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | —       | Yes |                                     | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| Investigation #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | —       | Yes |                                     | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| <p>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? N/A</p>                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| Investigation #1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | Yes |                                     | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| Investigation #2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | Yes |                                     | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| Investigation #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         | Yes |                                     | No |
| IND#:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |
| Explain:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |     |                                     |    |
| <p>c. Notwithstanding an answer of "yes" to (a) or (b), are there</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |     |                                     |    |

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:

BACK TO TOP

/S/

10.15.99

Signature of PM/CSO

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## PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21102 Trade Name: FEMHRT(ETHYL ESTRADIOL/NORETHINDRONE ACE  
Supplement Number: Generic Name: ETHYL ESTRADIOL/NORETHINDRONE ACETATE  
Supplement Type: Dosage Form:  
Regulatory Action: AP Proposed Indication: To prevent postmenopausal osteoporosis.

## ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

## What are the INTENDED Pediatric Age Groups for this submission?

       NeoNates (0-30 Days )        Children (25 Months-12 years)  
       Infants (1-24 Months)        Adolescents (13-16 Years)

Label Adequacy Does Not Apply  
Formulation Status  
Studies Needed  
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

## COMMENTS:

There is no indication that would involve use in any pediatric population. (10.15.99)

There is no need for any pediatric studies. The drug SHOULD not be used in children.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,  
ENID GALLIERS

Signature

/S/

Date

10.15.99

**ITEM 16.**  
**DEBARMENT CERTIFICATION**

Warner-Lambert Company hereby certifies that it is not debarred, and 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 this application.

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM TO FILE**

Subject: femhrt - NDA 21-102 (NDA 21-065)  
Final Labeling Negotiations  
Order of Tables in Medical Officer Review of NDA 21-102

From: Joanna K. Zawadzki, M.D.  
Division of Metabolic and Endocrine Drug Products

Date: 10/19/99

**Final Labeling Negotiations**

As noted in the NDA Review, a Telecon between the Division of Metabolic and Endocrine Drug Products (DMEDP) and the sponsor was held on 10/7/99. The Division firmly maintained that for safety reasons only the 1/5 mg norethindrone acetate/mcg ethinyl estradiol dosage would be approved. The sponsor held a Telecon with the Division of Reproductive and Urologic Drug Products on 10/8/99 and that Division was also willing to approve the 1/5 mg norethindrone acetate/mcg ethinyl estradiol dosage only. Another Telecon with the sponsor took place on 10/13/99 with both Divisions present. After this Telecon, the sponsor submitted revised physician and patient labeling for the 1/5 mg norethindrone acetate/mcg ethinyl estradiol dosage. There were several revisions of these labels, which were discussed jointly by both Divisions with the sponsor on 10/14/99. The major revision recommended by DMEDP after discussion with the statistician David Hoberman, Ph.D., was the presentation of the bone mineral density data: DMEDP recommended the use of "percent change in BMD" rather than [redacted] which the sponsor had selected. The reasons for the "percent change in BMD" selection were greater simplicity and greater analogy to other labels. In addition, DMEDP recommended comparing the placebo and 1/5 mg norethindrone acetate/mcg ethinyl estradiol dosage BMD percent change at 12 and 24 months, rather than comparing [redacted]

[redacted] This presentation of the data was clearer and closer to the actual objectives of the two-year clinical trial. Final agreement regarding the physician and patient labels was reached on 10/15/99 and the approval letter for the 1/5 mg norethindrone acetate/mcg ethinyl estradiol dosage (femhrt<sup>TM</sup>) was signed.

**Order of Tables in Medical Officer Review of NDA 21-102**

**Please note:** Many of the tables in the NDA review are copies of tables in the NDA. The original table numbers and titles are retained, though these tables are often not in the same order as in the original NDA.

Distribution of NDA 21-102 Medical Officer Review:  
Archival: HFD580/NDA 21-065; HFD580/Davis/Mann/Rarick/Spelllesane  
HFD510/Sobel/Troendle/Hoberman/Galliers/Zawadzki  
NDA 21-102; HFD-510/div. file

## **NDA 21-102 femhrt**

Clinical audits were conducted for NDA 21-065 at the request of DRUDP, and they included this NDA.

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Printed by Enid Galliers  
**Electronic Mail Message**

Date: 15-Oct-1999 01:24pm  
From: Ross Lobell  
ross.lobell@secure.aa.WL.com  
Dept:  
Tel No:

TO: Enid Galliers ( galliers@A1 )  
CC: Joanna Zawadzki ( zawadzki@A1 )  
Subject: NDA 21-102 Package Insert

Dear Enid:

I have inserted the new chart for Mean per cent change BMD. Rather than send a replacement page, I thought it would be easier to send the entire revised file. Dornette is out today and Diane Moore is filling in. She is not currently on secure e-mail. Could you forward a copy of this latest version to her as well.  
thanks.

<<FDA924 1-5 -oct1599Final .DOC>>

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following  
a ons on 10/15/99 13:24:08

[INFO] -- Access Manager:

This message was sent by Parke-Davis across the Internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

=====

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Printed by Enid Galliers  
**Electronic Mail Message**

Date: 15-Oct-1999 10:50am  
From: Ross Lobell  
ross.lobell@secure.aa.WL.com  
Dept:  
Tel No:

TO: Enid Galliers ( galliers@A1 )  
TO: Joanna Zawadzki ( zawadzki@A1 )

Subject: NDA 21-102 *PPI*

I have updated the PI's again this morning based on some additional minor comments from Dr. Davis. These 2 documents are attached. It is also being faxed to DRUDP this morning.

<<INFORMATION FOR THE PATIENT1014.doc>> <<FDA924 1-5 -oct1299  
alternative.DOC>>

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following  
annotations on 10/15/99 10:50:44

[INFO] - Access Manager:  
TI sage was sent by Parke-Davis across the Internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

=====

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WORLDWIDE REGULATORY AFFAIRS  
Sending Fax Number: (734) 622-RL

Pharmaceutical Research Division  
Warner-Lambert Company  
2800 Plymouth Road  
Ann Arbor, Michigan 48105  
USA

*If there is a problem with the transmission  
please call: (734) 622-*

PAGE 1 OF 2

---

TO: Dr. J. Zawadzki

FAX #: 301-443-9282

FROM: Ross Lobell

DATE: October 14, 1999

---

RE: NDA 21-102 24 month ITT adjusted mean BMD data

Dr. Zawadzki:

I believe the attached table is the one you are looking for. If not, please let me know so I can correct the table.

Thanks

Ross Lobell

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**NOTICE:** This facsimile is intended only for the use of the individual or entity to which it is addressed and may contain information that is privileged, confidential and exempt from disclosure. If the reader of this facsimile is not the intended recipient, or an employee or agent responsible for delivering the facsimile to the intended recipient, you are hereby notified that any review, disclosure, dissemination, distribution or copying of the communication is strictly prohibited. If you have received this communication in error, please notify the sender immediately at the telephone number(s) listed above and return the original facsimile to us at the above address by U.S. Mail, the cost of which will be reimbursed. Thank you.

Protocol 376-359

Adjusted Mean Percent Change from Baseline in Bone Mineral Density at Month 24

ITT Data: Corrected & Uncorrected

|                                      | Placebo      | NA/EE Treatment Group, mg/μg |             |             |             | EE Treatment Group, μg |              |             |             |
|--------------------------------------|--------------|------------------------------|-------------|-------------|-------------|------------------------|--------------|-------------|-------------|
|                                      |              | 0.2/1                        | 0.5/2.5     | 1/5         | 1/10        | 1                      | 2.5          | 5           | 10          |
| N                                    | 123          | 119                          | 120         | 124         | 118         | 119                    | 120          | 121         | 101         |
| Adjusted Mean<br>Percent Change (SE) | -4.57 (1.07) | -0.80 (1.09)                 | 0.68 (1.09) | 4.37 (1.07) | 6.01 (1.09) | -0.64 (1.09)           | -0.81 (1.08) | 0.60 (1.09) | 4.01 (1.18) |

APPEARS THIS WAY  
ON ORIGINAL

Printed by Enid Galliers  
**Electronic Mail Message**

Sensitivity: COMPANY CONFIDENTIAL

Date: 14-Oct-1999 08:56am  
From: Joanna Zawadzki  
ZAWADZKIJ  
Dept: HFD-510 PKLN 14B04  
Tel No.: 301-827-6430 FAX 301-443-9282

TO: Enid Galliers  
TO: Gloria Troendle  
TO: Solomon Sobel

( GALLIERS )  
( TROENDLE )  
( SOBEL )

CC: Daniel Davis  
CC: Marianne Mann  
CC: Dornette Spell-LeSane  
Subject: Labeling Changes

( DAVIS )  
( MANN )  
( SPELLLESANED )

Good morning.

My labeling changes for femhrt are attached. HFD-580 relayed their changes to the sponsor yesterday. I will talk with Dan this morning to coordinate our changes with those made by HFD-580.

Thanks.

Joanna

/S/

/S/

/S/

/S/

10:25 AM 10/14/99  
T-con

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ON ORIGINAL

23 Page(s) Redacted

Draft

Labeling

® PARKE-DAVIS

DUPLICATE

October 13, 1999

NDA 21-102

Ref. No. 004

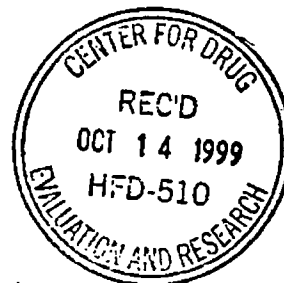
femhrt™ (norethindrone acetate and ethinyl  
estradiol) Tablets

NEW CORRESP

NC

Re: Response to FDA Request for  
Information

Solomon Sobel, M.D.  
Director  
Division of Metabolism and Endocrine  
Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Attention: Document Control Room 14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



Dear Dr. Sobel:

We refer to our files for NDA 21-102, for femhrt™ (norethindrone acetate and ethinyl estradiol) Tablets, and to the request made by Ms. Enid Galliers of your Division for the following:

1. Provide a copy of the BMD table provided on October 7, 1999.
2. Provide a list of Parke-Davis attendees for the October 7, 1999 telephone conference with DMEDP.

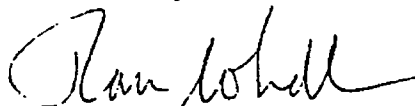
The requested table is attached. The Parke-Davis attendee list is given below:

|                        |                    |
|------------------------|--------------------|
| Randall Whitcomb, M.D. | Drug Development   |
| Barbara Gillman        | Drug Development   |
| Rochelle Hanley, M.D.  | Clinical           |
| James Symons, Ph.D.    | Clinical           |
| Mary O'Keefe           | Biostatistics      |
| Mary Taylor, MPH       | Regulatory Affairs |
| Ross Lobell            | Regulatory Affairs |
| Andrew Panagy          | Marketing          |
| Elizabeth Attias       | Marketing          |

Solomon Sobel, M.D.  
NDA 21-102  
October 13, 1999  
Page 2

Should you have any questions or comments regarding this submission, please contact me at 734/622-2111 or send a facsimile to 734/622-3283.

Sincerely,



Ross Lobell  
Senior Manager  
Worldwide Regulatory Affairs

Desk Copy: Dr. Joanna Zawadzki (HFD-510)

RL:kb  
10-13-1999\RN-004\21-102\CI-0376\Letter

Attachment

APPEARS THIS WAY  
ON ORIGINAL

Protocol 376-359  
Bone Mineral Density Summary  
ITT Data, Month 12: Corrected & Uncorrected

|                                                | NA/EE Treatment Group, mg/μg |               |               |               |               | EE Treatment Group, μg |               |               |               |  |
|------------------------------------------------|------------------------------|---------------|---------------|---------------|---------------|------------------------|---------------|---------------|---------------|--|
|                                                | Placebo                      | 0.2/1         | 0.5/2.5       | 1/5           | 1/10          | 1                      | 2.5           | 5             | 10            |  |
| N                                              | 112                          | 109           | 115           | 117           | 112           | 115                    | 118           | 117           | 99            |  |
| Baseline Mean (SE), mg/cc                      | 119.50 (2.19)                | 119.24 (1.70) | 119.63 (1.91) | 117.81 (1.64) | 119.74 (1.95) | 119.50 (1.76)          | 116.99 (1.65) | 118.68 (1.79) | 120.13 (1.99) |  |
| Follow-up Mean (SE), mg/cc                     | 115.86 (2.34)                | 117.40 (1.88) | 119.27 (1.86) | 122.30 (1.82) | 125.41 (2.07) | 118.66 (2.01)          | 116.05 (1.70) | 117.82 (1.96) | 123.22 (2.09) |  |
| Change from baseline (SE), mg/cc               | -3.65 (0.92)                 | -1.84 (1.05)  | -0.35 (1.35)  | 4.49 (0.88)   | 5.67 (1.12)   | -0.84 (1.04)           | -0.94 (0.86)  | -0.85 (1.02)  | 3.09 (0.91)   |  |
| Percent change from baseline (SE)              | -3.25 (0.85)                 | -1.47 (0.89)  | 0.69 (1.20)   | 3.83 (0.80)   | 5.24 (0.98)   | -0.71 (0.89)           | -0.58 (0.76)  | -0.54 (0.88)  | 2.87 (0.82)   |  |
| Adjusted Mean                                  | -2.73 (1.02)                 | -1.32 (1.04)  | 0.24 (1.00)   | 4.99 (0.99)   | 6.29 (1.01)   | -0.37 (1.00)           | -0.51 (0.98)  | -0.14 (1.00)  | 3.49 (1.06)   |  |
| Change from baseline <sup>a</sup> (SE)         |                              |               |               |               |               |                        |               |               |               |  |
| Adjusted Mean                                  | -2.49 (0.90)                 | -1.01 (0.92)  | 1.28 (0.89)   | 4.31 (0.88)   | 5.77 (0.90)   | -0.24 (0.89)           | -0.20 (0.87)  | 0.08 (0.89)   | 3.22 (0.95)   |  |
| Percent change from baseline <sup>a</sup> (SE) |                              |               |               |               |               |                        |               |               |               |  |

Analyses based on Adjusted Mean

|                                                                |        |           |          |          |          |           |           |           |          |  |
|----------------------------------------------------------------|--------|-----------|----------|----------|----------|-----------|-----------|-----------|----------|--|
| Percent change from baseline                                   |        |           |          |          |          |           |           |           |          |  |
| p-value <sup>b</sup> (NA/EE or EE vs. Placebo)                 | --     | 0.2898    | 0.0038   | 0.0001   | 0.0001   | 0.0987    | 0.0903    | 0.0549    | 0.0001   |  |
| 95% Confidence Interval <sup>c</sup> (NA/EE or EE vs. Placebo) | --     | [-1.2, ∞] | [1.1, ∞] | [4.2, ∞] | [5.6, ∞] | [-0.4, ∞] | [-0.3, ∞] | [-0.0, ∞] | [3.0, ∞] |  |
| p-value <sup>d</sup> (Follow-up vs. Baseline)                  | 0.0061 | 0.2739    | 0.1532   | 0.0001   | 0.0001   | 0.7849    | 0.8140    | 0.9240    | 0.0007   |  |
| p-value <sup>e</sup> (NA/EE vs EE)                             | --     | 0.5317    | 0.2188   | 0.0004   | 0.0443   | --        | --        | --        | --       |  |

<sup>a</sup> Adjusted for treatment group, center, and baseline

<sup>b</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.

<sup>c</sup> For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

<sup>d</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>e</sup> The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

APPEARS THIS WAY  
ON ORIGINAL

**Meeting Objectives:**

1. To discuss the "participants report of bleeding" data in the proposed label.
2. To discuss the approvability of the [redacted]

**Background:**

The sponsor was informed during a teleconference September 29, 1999, by DRUDP of the questionable approvability of the [redacted] the sponsor received labeling changes omitting the [redacted] from the osteoporosis indication from DMEDP followed by a teleconference discussing this issue on October 7, 1999; the sponsor submitted arguments to support the [redacted] on October 12, 1999; FDA requested a teleconference with the sponsor to convey the decision based on review of the information submitted.

**Discussion:**

**Issue #1: Reporting vaginal bleeding/spotting data in the label**

**Sponsor:**

- the reporting of 3-month data in the label is useful information for physicians when assessing patients and educating them regarding the potential for irregular bleeding as a result of starting femhrt

**FDA:**

- 3-month data is not an accurate report of bleeding; 12-month data is most relevant; a chart/graph is acceptable to demonstrate the cumulative effect that would allow for interpretation of bleeding occurring during the first year; patients are most concerned with bleeding over time

**Issue #2: Approvability of the [redacted]**

**Decisions made:**

- [REDACTED]
- 1/5 is the lowest effective dose for femhrt

**Action Items:**

Sponsor to submit draft label by 3:00 p.m., 10/13/99

/S/

Minutes Preparer

/S/

Concurrence, Chair

10/29/99

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ON ORIGINAL

Bi

Printed by Enid Galliers  
**Electronic Mail Message**

Date: 13-Oct-1999 02:55pm  
From: Ross Lobell  
ross.lobell@secure.aa.WL.com  
Dept:  
Tel No:

TO: 'SPELLLESANED@SECURE.CDER.FDA.GOV' ( SPELLLESANED@A1 )  
TO: Enid Galliers ( galliers@A1 )  
TO: Joanna Zawadzki ( zawadzki@A1 )

Subject: NDA 21-065, NDA 21-102 femhrt Package Insert

Attached is the revised femhrt package insert based upon this mornings telephone conference. I have highlighted new language in blue. The graphs and table in the pk section have been removed since they refer to the [redacted] The reference to the [redacted] has also been removed.

In modifying figure 1, the background changed. I didn't have enough time to figure out why. The shading will not be present in the final printed insert.

<<FDA924 1-5 -oct1299 alternative.DOC>>

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following annotations on 10/13/99 14:55:01

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ON ORIGINAL

CC: Orig NDA 21-102  
HPD-510/div file

## Teleconference Minutes

**Date:** October 13, 1999

**Time:** 10:30-11:30 a.m.

**Location:** Parklawn; Rm. 17B-43

**NDA:** 21-065

**Drug:** Femhrt (norethindrone acetate and ethinyl estradiol)

**Indication:** Hormone Replacement Therapy

**Sponsor:** Parke-Davis Pharmaceutical

**Type of Meeting:** Guidance

**Meeting Chair:** Marianne Mann, M.D.

**External Lead:** Ross Lobell

**Meeting Recorder:** Dornette Spell-LeSane, NP-C

### **FDA Attendees:**

Lisa Rarick, M.D., Division Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)

Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)

Dan Davis, MD, Medical Officer, DRUDP (HFD-580)

Gloria Troendell, M.D., Deputy Director, Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

Joanna Zawadzki, Medical Officer, DMEDP (HFD-510)

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @DRUDP (HFD-580)

Venkateswar Jarugula, Ph.D., Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II DPE II @ DRUDP (HFD-580)

David Hoberman, Statistician, Division of Biometrics II @ DRUDP (HFD-580)

Enid Galliers, Chief Project Management Staff, DMEDP (HFD-510)

Terri Rumble, Chief Project Management Staff, DRUDP (HFD-580)

Dornette Spell-LeSane, Project Manager, DRUDP (HFD-580)

### **External Attendees:**

Ross Lobell, Manager, Regulatory Affairs

Mary Okeeth, Statistician

Mary Taylor, Regulatory affairs

Jim Symons, Clinical group

Rochelle Hannley, Clinical Group

Rebecca Boyd, Pharmacokinetics

Beth Attias, Marketing

Andy Panagy, Marketing

Randall Whitcomb, Drug Development

Byron Scott, Regulatory Affairs

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE SENT:** October 12, 1999

**DUE DATE:** N/A

**OPDRA CONSULT #:** 99-055

**TO (Divisions):**

Lisa Rarick, MD  
Director, Division of Reproductive and Urologic Drug Products  
HFD-580

Solomon Sobel, MD  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**PRODUCT NAME:** femhrt

**MANUFACTURER:** Parke-Davis

**NDA #:** 21-065

**CASE REPORT NUMBER(S):** Not applicable.

**SUMMARY:**

In response to consults from the Division of Reproductive and Urologic Drug Products and Division of Metabolism and Endocrine Drug Products, OPDRA conducted a review of the proposed proprietary name femhrt to determine the acceptability based on potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:**

Since the Divisions permitted the firm to utilize the proprietary name "femhrt", OPDRA recommends the use of the phonetic spelling in conjunction with the proprietary name to eliminate the potential risk of cardiac promotional claims.

*/S/* 10/12/99  
Jerry Phillips  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 827-5189

*/S/* 10/13/99  
Peter Honig, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

cc:  
Orig  
NDA 21-106  
HFD-50/  
div. files

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm 15B03  
Center for Drug Evaluation and Research**

**MEDICATION ERROR REVIEW**

**DATE OF REVIEW:** October 6, 1999  
**NDA#** 21-065  
**NAME OF DRUG:** femhrt (Norethindrone Acetate and Ethinyl Estradiol Tablets, USP)  
**NDA HOLDER:** Parke-Davis

**I. INTRODUCTION:**

On October 4, 1999, the Division of Metabolic and Endocrine Drug Products (HFD-510) requested OPDRA evaluate the proposed proprietary name "femhrt" for NDA 21-065 manufactured by Parke-Davis.

Originally the tradename was proposed as FemHRT. The Division reported the LNC committee reviewed this proprietary name on October 1, 1996 during the IND phase and the committee rendered the following decision:

"The Committee found no look-alike/sound-alike conflicts or any misleading and fanciful aspects with the proposed proprietary name. The Committee does wonder how this name is to be pronounced. The LNC has no reason to find the proposed name unacceptable."

The Division sent a consult for reassessment of the tradename on September 27, 1999 as an NDA and stated the sponsor has on numerous occasions pronounced the tradename as "FemHeart". The LNC Committee rereviewed the name and rendered the following decision:

"The Committee felt the name is too close to Femstat (OTC product) and [redacted] (Rx). Additionally, the DDMAC representative is uncomfortable with the name implying a therapeutic indication (hormone replacement therapy). They also have misgivings about the inexact pronunciation and the possibility of "heart" being co-promoted. The LNC finds the name unacceptable."

On September 29, 1999, the Division informed the firm that the proposed name was unacceptable. On September 30, 1999 the firm contacted the Director, Office of Review Management and expressed their objections to the decision on the proposed name.

On October 3, 1999, the Division of Reproductive and Urologic Drug Products and the Division of Metabolism and Endocrine Drug Products met to discuss the appropriate name for this combination product. The Divisions decided to allow Parke-Davis to utilize "femhrt" as the proprietary name thinking it would likely be pronounced "fem-hert" rather than "fem-heart". The firm objected because they had already preprinted the foil lining of the tablets with "FemHRT" and stated it would be very costly and pose a 6 month delay in getting their product to the market and therefore was unfairly burdensome. Parke-Davis suggested that they be permitted to initially market their product as

"FemHRT" but they would commit to changing all packaging with the FDA's suggestion of "femhrt" as soon as possible or within 6 months. The Divisions did not agree with this proposal because they remained concerned that the product name would be fairly well established in the first 6 months of marketing as "FemHRT". The Divisions requested the firm change the name to "femhrt" immediately for all packaging and promotional materials but clarified that we could accept the inner foil reading "femHRT" until the new foil could be printed.

## II. SAFETY AND RISK ASSESSMENT:

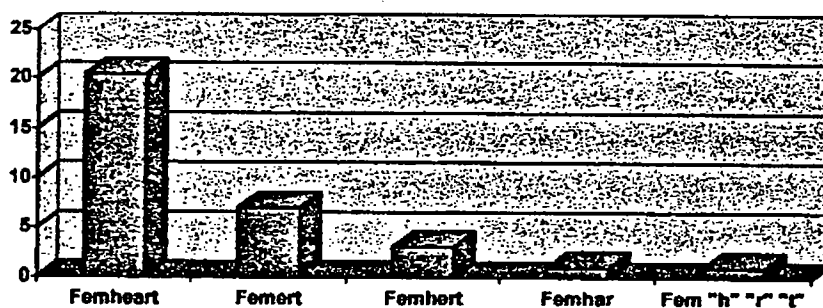
1. An internal study was conducted within OPDRA to evaluate the proposed proprietary name and determine how the proposed name would be pronounced. This analysis was conducted to determine if the new presentation of the name would still have the connotation of "heart" associated with it.

### Methodology:

A study was conducted for the proposed name "femhrt" involving 14 health care practitioners within OPDRA. The participants were comprised of pharmacists, physicians and nurses. Participants were contacted via phone and e-mail. The first group contacted, via telephone, were informed OPDRA had an established name they were evaluating and wanted their interpretation of the name pronunciation. The name was then spelled "femhrt", at that point every participant questioned the spelling of the proposed name. OPDRA stated the spelling was correct and they in turn provided their verbal interpretation of the pronunciation of the proposed name. The second group of participants were e-mailed and informed that OPDRA had a proprietary name "femhrt" that they were evaluating and needed their interpretation of the name pronunciation. Each individual was instructed to telephone OPDRA with their response.

### Results:

Thirteen out of fourteen individuals responded to the survey. 1% responded with the name pronunciation that the Division most likely expected, "femhert". 54% responded with the pronunciation of "femheart". 23% responded with "femert", 1 % responded with "Femhar" and 1% responded with [Fem "h" "r" "t"].



### Analysis:

54% of the participants pronounced the drug name "femheart". Most participants stated the spelling of the drug name made no sense to them and did not appear to be grammatically correct and needed to confirm the spelling prior to providing their responses. The responses did not contain any names that had the potential to be confused with any approved or pending drug products. The decrease in the prominence of "hrt" appears to not have made a significant difference in the pronunciation of the name. Most health care practitioners will probably pronounce "femhrt" as "femheart". These

findings substantiate the Division's original concerns when the name was originally proposed as "FemHRT".

2. A search of the American Drug Index (43rd Edition), Physicians' Desk Reference [53 Edition; 1999] and Drug Facts and Comparisons (Updated Monthly) for potential sound-alike or look-alike names to approved drugs was completed. The findings were discussed in a focal group within OPDRA.

In OPDRA's opinion, [redacted] and Femstat, could possibly pose a problem with confusion when written. OPDRA believes a written analysis would be needed to assess the degree to which these proprietary names might be confused. (i.e., overlapping strengths, etc.). Written analysis studies require more review time and due to time constraints with this review, a written analysis was not performed.

3. A search of the Agency's internal databases, Establishment Evaluation System (EES), Drug Product Reference File (DPR), and the Labeling and Nomenclature Committee database (LNC) for potential sound-alike or look-alike names to unapproved/approved drugs did not reveal any potential problems with sound-alike/look-alike issues.

### III. RECOMMENDATIONS:

1. From a safety perspective, OPDRA believes the use of the proposed proprietary name "femhrt" poses no significant safety risk.
2. After review of the results of the study, OPDRA concludes "femhrt" will most likely be pronounced as "femheart". From a promotional perspective, OPDRA believes this is unacceptable. The firm may possibly promote cardiac claims given "heart" is associated with the pronunciation of the name. In addition, the name may also be considered misleading in that it implies some effect on the "heart".
3. We recognize the Division's decision to accept the name "femhrt". If this name is utilized, OPDRA recommends the firm be requested to introduce the phonetic spelling of the pronunciation of "femhrt" on promotional, carton and insert labeling (i.e. fem ert). This might diminish the likelihood of mispronunciation of the name as "femheart" and hopefully help eliminate the concerns surrounding the cardiac promotional claims.

**APPEARS THIS WAY  
ON ORIGINAL**

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

/S/

Carol Holquist, RPh  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

10/12/99

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files  
HFD-510; Lanh Green, Safety Evaluator, DDRE II, OPDRA  
HFD-580; Denise Toyer, Safety Evaluator, DDRE II, OPDRA  
HFD-400; Jerry Phillips, Associate Director, OPDRA  
HFD-400; Peter Honig, Deputy Director, OPDRA  
HFD-002; Murray Lumpkin, Acting Director, OPDRA

APPEARS THIS WAY  
ON ORIGINAL

Printed by Enid Galliers  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 07-Oct-1999 06:02pm  
**From:** Dornette Spell-LeSane  
SPELLLESANED  
**Dept:** HFD-580 PKLN 17B45  
**Tel No:** 301-827-4260 FAX 301-827-4267

|                          |               |
|--------------------------|---------------|
| TO: Marianne Mann        | ( MANNM )     |
| TO: Daniel Davis         | ( DAVISD )    |
| TO: Michael Ortwerth     | ( ORTWERTHM ) |
| TO: Venkateswar Jarugula | ( JARUGULAV ) |
| TO: Enid Galliers        | ( GALLIERS )  |
| TO: Joanna Zawadzki      | ( ZAWADZKIJ ) |

**Subject:** FWD: femhrt PPI

APPEARS THIS WAY  
ON ORIGINAL

Printed by Enid Galliers  
**Electronic Mail Message**

**Date:** 07-Oct-1999 04:00pm  
**From:** Karen Lechter  
LECHTERK  
**Dept:** HFD-42 PKLN 17B04  
**Tel No:** 301-827-2828 FAX 301-594-6759

**Subject:** femhrt PPI

Attached is the femhrt PPI. Sorry it took so long. We had some unexpected emergencies. Please distribute it to the appropriate team members. I will bring you a signed copy.

Please let me know if you have questions. I will be out of the office on Friday, but I will be in on Tuesday.

Thanks  
Karen

APPEARS THIS WAY  
ON ORIGINAL

Printed by Enid Galliers  
**Electronic Mail Message**

Date: 07-Oct-1999 09:02am  
 From: Ross Lobell  
 ross.lobell@secure.aa.WL.com  
 Dept:  
 Tel No:

TO: Enid Galliers ( galliers@A1 )

Subject: NDA 21-102, femhrt

Dear Ms. Galliers:

In your labeling comments of October 1, 1999 you had included a request for Intent-To-Treat analysis at 12 months for BMD.

This information is presented below (the table is quite wide, it will be best viewed on full screen):

Protocol 376-359  
 Bone Mineral Density Summary  
 ITT Data, Month 12: Corrected & Uncorrected

| mg                                              | NA/EE Treatment Group, mg/mg |       |         |               |              | EE Treatment Group, |     |              |
|-------------------------------------------------|------------------------------|-------|---------|---------------|--------------|---------------------|-----|--------------|
|                                                 | Placebo                      | 0.2/1 | 0.5/2.5 | 1/5           | 1/10         | 1                   | 2.5 | 5            |
| 10                                              |                              |       |         |               |              |                     |     |              |
| N                                               | 112                          | 109   | 115     | 117           | 112          | 115                 | 118 | 117          |
| 91                                              |                              |       |         |               |              |                     |     |              |
| Baseline Mean (SE), mg/cc                       | 119.50 (2.19)                |       |         | 119.24 (1.70) |              | 119.63              |     |              |
| (1.91)                                          | 117.81 (1.64)                |       |         | 119.74 (1.95) |              | 119.50 (1.76)       |     | 116.99       |
| (1.65)                                          | 118.68 (1.79)                |       |         | 120.13 (1.99) |              |                     |     |              |
| Follow-up Mean (SE), mg/cc                      | 115.86 (2.34)                |       |         | 117.40 (1.88) |              | 119.27              |     |              |
| (1.86)                                          | 122.30 (1.82)                |       |         | 125.41 (2.07) |              | 118.66 (2.01)       |     | 116.05       |
| (1.70)                                          | 117.82 (1.96)                |       |         | 123.22 (2.09) |              |                     |     |              |
| Change from baseline (SE), mg/cc                |                              |       |         | -3.65 (0.92)  | -1.84 (1.05) |                     |     |              |
| -0.35 (1.35)                                    | 4.49 (0.88)                  |       |         | 5.67 (1.12)   |              | -0.84 (1.04)        |     |              |
| -0.94 (0.86)                                    | -0.85 (1.02)                 |       |         | 3.09 (0.91)   |              |                     |     |              |
| Percent change from baseline (SE)               |                              |       |         | -3.25 (0.85)  | -1.47 (0.89) | 0.69                |     |              |
| (1.20)                                          | 3.83 (0.80)                  |       |         | 5.24 (0.98)   |              | -0.71 (0.89)        |     | -0.58 (0.76) |
| -0.54 (0.88)                                    | 2.87 (0.82)                  |       |         |               |              |                     |     |              |
| Adjusted Mean Change from baseline (SE)         |                              |       |         | -2.73 (1.02)  |              | -1.32 (1.04)        |     |              |
| 0.24 (1.00)                                     | 4.99 (0.99)                  |       |         | 6.29 (1.01)   |              | -0.37 (1.00)        |     |              |
| -0.51 (0.98)                                    | -0.14 (1.00)                 |       |         | 3.49 (1.06)   |              |                     |     |              |
| Adjusted Mean Percent change from baseline (SE) |                              |       |         | -2.49 (0.90)  |              |                     |     |              |
| -1.01 (0.92)                                    | 1.28 (0.89)                  |       |         | 4.31 (0.88)   |              | 5.77 (0.90)         |     |              |
| -0.24 (0.89)                                    | -0.20 (0.87)                 |       |         | 0.08 (0.89)   |              | 3.22 (0.95)         |     |              |

Analyses based on Adjusted Mean Percent change from baseline

|                                                                |           |          |        |           |
|----------------------------------------------------------------|-----------|----------|--------|-----------|
| p-value <sup>b</sup> (NA/EE or EE vs. Placebo)                 | -         | 0.2898   | 0.0038 | 0.0001    |
| 0.0001                                                         | 0.0987    | 0.0903   | 0.0549 | 0.0001    |
| 95% Confidence Interval <sup>c</sup> (NA/EE or EE vs. Placebo) | -         |          |        | [-1.2, 7] |
| [1.1, 7]                                                       | [4.2, 7]  | [5.6, 7] |        |           |
| [-0.3, 7]                                                      | [-0.0, 7] | [3.0, 7] |        |           |
| p-value <sup>d</sup> (Follow-up vs. Baseline)                  | 0.0061    | 0.2739   | 0.1532 | 0.0001    |
| 0.0001                                                         | 0.7849    | 0.8140   | 0.9240 | 0.0007    |
| p-value <sup>e</sup> (NA/EE vs EE)                             | -         | 0.5317   | 0.2188 | 0.0004    |
| -                                                              | -         | -        | -      | 0.0443    |

a Adjusted for treatment group, center, and baseline

b The null hypothesis is that the mean change in the NA/EE or EE treatment group is <= to the mean change in the placebo group.

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c For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

d The null hypothesis is that the mean change from baseline is equal to zero

e If hypothesis is that the mean change in the NA/EE and corresponding treatment groups are equal.

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-1111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following annotations on 10/07/99 09:00:29

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[INFO] - Access Manager:

This message was sent by Parke-Davis across the Internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

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APPEARS THIS WAY  
ON ORIGINAL

NDA 21-102 FemHRT  
(norethindrone acetate[NA]/ethinyl estradiol[EE] tablets)

October 7, 1999  
Parke-Davis  
10:30 - 11:30 AM

### MEMORANDUM OF TELECON

**FDA Participants:**

Gloria Troendle, MD, Deputy Director, DMEDP  
Joanna Zawadzki, MD, Medical Officer, DMEDP  
Enid Galliers, CPMS, DMEDP

**Parke-Davis Participants:**

Randall Whitcomb, MD, Drug Development  
Barbara Gillman, Drug Development  
Rochelle Hanley, MD, Clinical  
James Symons, Ph.D., Clinical  
Mary O'Keefe, Biostatistics  
Mary Taylor, MPH, Director, Worldwide Regulatory Affairs  
Ross Lobell, Senior Manager, Worldwide Regulatory Affairs  
Andrew Panagy, Marketing  
Elizabeth Attias, Marketing

**Purpose:** To discuss osteoporosis-related changes to labeling that DMEDP had sent to Parke-Davis (PD) by secure email on October 1 and 6, 1999.

**Discussion:** DMEDP reiterated the reasons for the changes that had been requested.

Parke Davis referred to the DMEDP request to remove information regarding the [REDACTED]  
[REDACTED] The firm asked DMEDP to  
explain the rationale for not approving the [REDACTED] (DMEDP noted that there are  
[REDACTED]  
[REDACTED]

Parke Davis said that the labeling revised according to DMEDP's two recent requests would be submitted the next day.

NDA 21-102 Telecon October 7, 1999 10:30 AM  
Page 2

/S/

Enid Galliers, CPMS, DMEDP

Cc: Orig. NDA 21-102  
HFD-510/div. Files  
HFD-510/JZawadzki, GTroendle, EGalliers

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ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

---

DATE: October 6, 1999  
FROM: Karen Lechter, HFD-40  
TO: Dornette Spell-LeSane  
SUBJECT: femhrt  
NDA 21-065

I have reviewed the proposed PPI for this combination estrogen/progestin product and have discussed my comments with Lisa Stockbridge. She suggested some additional changes that I have incorporated here. I will summarize the major suggestions in this memorandum. I have attached a proposed PPI.

I have moved some information to keep similar information together. I have made some changes to the language to simplify it, have inserted some new section headings, and renamed others. I have removed redundant information. These changes were made to make the material easier for readers to follow.

Your division should review my suggestions before forwarding them to the sponsor, to be sure you agree with these proposals. I inserted some new information that you may not want to keep, including the following:

- a comment that the doctor may ask patients to take vitamin D along with calcium ("Other Information")
- instructions on what to do if a dose is missed ("How should I take femhrt?")
- instructions on when to take the medication ("How should I take femhrt?")
- advice to get a mammogram once a year if you are age 50 or above ("What are the possible side effects of femhrt?")

I have removed the following:

If I had had more time, I could have given you a copy of the PPI with strikeouts and additions well marked. However, due to time constraints, I was unable to do this.

Please let me know if you have any questions.

**APPEARS THIS WAY  
ON ORIGINAL**

cc:  
HFD-40/Lechter/Ostrove/Reading/Stockbridge  
NDA 21-065

KLlechter 10/6/99; Stockbridge 10/7/99; Lechter 10/7/99

**APPEARS THIS WAY  
ON ORIGINAL**

5 Page(s) Redacted

Draft

Labeling

Printed by Enid Galliers  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL      **Date:** 06-Oct-1999 01:41pm  
**From:** Enid Galliers  
          GALLIERS  
**Dept:** HFD-510                      PKLN 14B04  
**Tel No:** 301-827-6429 FAX 301-443-9282

**TO:** ross.lobell@secure.aa.wl.com

**Subject:** N21-102 Tx PMO-related labeling changes (10/06/99)-JZ

**Ross:**

The osteoporosis-related labeling changes - with our rationale - are in the attachment.

Dr. Z hopes we can still discuss them tomorrow at 10:30 AM. Please advise.

Thanks,

Enid

**APPEARS THIS WAY  
ON ORIGINAL**

2 Page(s) Redacted

Draft

Labeling

Printed by Enid Galliers  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 06-Oct-1999 07:26am  
**From:** Dornette Spell-LeSane  
SPELLLESANED  
**Dept:** HFD-580 PKLN 17B45  
**Tel No:** 301-827-4260 FAX 301-827-4267

|                                 |                  |
|---------------------------------|------------------|
| <b>TO:</b> Michael Ortwerth     | ( ORTWERTHM )    |
| <b>TO:</b> Venkateswar Jarugula | ( JARUGULAV )    |
| <b>TO:</b> Moo-Jhong Rhee       | ( RHEEM )        |
| <b>TO:</b> Joanna Zawadzki      | ( ZAWADZKIJ )    |
| <b>TO:</b> Enid Galliers        | ( GALLIERS )     |
| <b>TO:</b> Lisa Stockbridge     | ( STOCKBRIDGEL ) |

**Subject:** FWD: Proposal from Parke-Davis for t-con 10/6/99

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ON ORIGINAL

# BEST POSSIBLE COPY

## Printed by Enid Galliers Electronic Mail Message

Date: 05-Oct-1999 03:10pm  
From: Dornette Spell-LeSane  
SPELLLESANED  
Dept: HFD-580 PKLN 17B45  
Tel No: 301-827-4260 FAX 301-827-4267

Subject: Proposal from Parke-Davis for t-con 10/6/99

Hello Everyone,

I wanted to summarize for you Park-Davis proposal to be considered and discussed at the teleconference Wednesday 10/6/99 at 2 p.m. 17B43. Marianne, John Jenkins, and Florence Houn will be attending the meeting. For others, If you would like to attend please feel free. You may respond by e-mail with comments you would like conveyed at the meeting.

1. Parke-Davis agrees to change all promotional materials to reflect the change to femhrt.
2. Parke-Davis would like to peruse the recommendation by the Division to maintain "Fem-HRT" on the foil primary packaging blister (secondary packaging) for at least 6-months.
3. Changing the carton labeling and printed labeling to reflect the change from fem-HRT to femhrt has become more challenging. Doing this would delay the launch and the packaging is expected to arrive in 2 weeks. Parke-Davis proposes to use the fem-HRT as stated in their current draft labeling, making the change to the new femhrt in April 2000 at next printing.

L : Spell-LeSane, PM

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ON ORIGINAL

## Meeting Minutes

**Date:** October 4, 1999

**Time:** 4:00 - 5:05 PM

**Place:** Parklawn; Rm. 13B-45

**Type of Meeting:** Internal discussion

**NDA:** 21-065

**Drug Name:** femhrt (1.0 mg norethindrone acetate and 5.0 mcg ethinyl estradiol) Tablets

**NDA:** 21-102

**Drug Name:** femhrt (1.0 mg norethindrone acetate and 5.0 mcg ethinyl estradiol) Tablets

**Indications:** NDA 21-065- treatment of moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause  
NDA 21-102- prevention of osteoporosis

**Sponsor:** Parke-Davis Pharmaceuticals

**NDA:** [REDACTED]

**NDA:** [REDACTED]

**FDA Lead:** Dr. Florence Houn

**Meeting Recorder:** Ms. Diane Moore

### FDA Participants:

Florence Houn, M.D., M.P.H. - Office Director, ODE III (HFD-103)

Victor Raczkowski, M.D. - Deputy Office Director, ODEIII (HFD-103)

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Dan Davis, M.D., - Medical Officer, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Regulatory Project Manager, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C. - Regulatory Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Michael Ortwerth, Ph.D. - Review Chemist, DNDC II @ DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

John Jenkins, M.D. - Office Director, ODE II (HFD-102)

Lee Ripper - Associate Office Director, ODE II (HFD-102)

Sol Sobel, M.D. - Director, Division of Metabolic and Endocrine Drug Products (DMEDP; HFD 510)

Leo Lutwak, M.D. - Medical Officer, DMEDP (HFD-510)

Meeting Minutes – October 4, 1999

Joanna Zawadzki, M.D. – Medical Officer, DMEDP (HFD-510)

Enid Galliers – Chief, Project Management Staff, DMEDP (HFD-510)

Maureen Hess, MPH, R.D. – Regulatory Project Manager (DMEDP; HFD-510)

Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and Communication (DDMAC; HFD-42)

Sammie Beam, R.Ph. - Project Manager, Office of Pharmacology Drug Review (OPDRA; HFD-400)

Carol Pamer – Safety Evaluator, Medical Errors Staff (HFD-400)

**Meeting Objective:** To discuss the status and handling of four NDAs that are currently being reviewed in both DRUDP and DMEDP.

**Background:** NDA 21-065 was submitted to DRUDP for the indications of VMS [redacted] and osteoporosis. The osteoporosis indication was unbundled and sent to DMEDP as a Type 6 NDA (NDA 21-102). Once the review of NDA 21-102 has been completed, the NDA will be rolled into NDA 21-065 as an efficacy review and NDA 21-102 will be retired.

[redacted]

**Discussion Items relevant to NDAs 21-065 and 21-102:**

- the Tradename, "FemHRT" was found to be acceptable by the labeling and nomenclature committee (LNC) in 1996; during the current NDA review cycle, the tradename was reviewed at the Office Level and was found to be unacceptable
  - there was concern that the "HRT" part of the word could be interpreted as "heart" and, therefore, imply a claim to improve the health of the heart, a claim that has not been addressed by any studies with this product
  - the sponsor contacted Dr. Lumpkin regarding this decision; a compromise has been proposed to use the same letters, but they must all be the same size, font, color and written in lower case (femhrt)
  - in addition, the sponsor requested that they be allowed to use internal blister-foil packaging they have already printed which uses the previous name (FemHRT) for six months; the Division agreed that the sponsor could use the FemHRT printing on only the aluminum packaging and all other labels must use the lower case (femhrt); FemHRT cannot be used in any promotional materials; this topic is still under discussion and negotiation with the sponsor
  - the name is pronounced "femert"
- the sponsor is seeking to remove the [redacted]; the sponsor seeks approval of the 1/5 and [redacted]
  - DRUDP and DMEDP are considering approval of the 1 mg norethindrone acetate/5 mcg ethinyl estradiol dose for the treatment of VMS and prevention of osteoporosis indications
  - the 1/5 dose will not be approved for the [redacted] because inadequate objective data was provided to prove the efficacy of the drug product for this indication

[redacted]

- a teleconference is scheduled for October 6, 1999, with Parke-Davis to discuss the tradename issue

Discussions relevant to NDAs

[redacted]

Decisions:

- [redacted]
- the sponsor should provide an updated label
- representatives from OPDRA should be included in the labeling meetings
- action packages for NDA 21-065 and [redacted] will be circulated in DRUDP and action packages 21-102 and [redacted] will be circulated in DMEDP
- there will be one combined label for NDA 21-065 and NDA 21-102 to include both the VMS and osteoporosis indications
- [redacted]

NDA 21-065

Page 4

NDA 21-102

NDA [redacted]

NDA [redacted]

Meeting Minutes – October 4, 1999

- there will be one combined letter for NDA 21-065 and NDA 21-102; this letter will contain the signatures from both DRUDP and DMEDP Division Directors

[redacted]

• Action items:

• Item Responsible Person: Date Due:

[redacted]

[redacted] /S/ 11/5/99  
Signature, minutes preparer

[redacted] /S/ 11/5/99  
Signature, Chair

Concurrence:

KColangelo, TRumble 10.19.99

TRumble, LKammerman, MOrtwerth, FHoun, JJenkins, MMann, LLutwak, MHess, JZawadzki  
10.26.99/DSpell-LeSane, DDavis 10.27.99/MRhee 11.04.99/LRarick, VJarugula, 11.05.99

Concurrence not received from VRaczkowski, LRipper, SSobel, EGalliers, SBeam, CPamer

cc:

HFD 510

HFD 580

HFD-580/attendees

HFD 510/attendees

[redacted] /S/ 11/8/99

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gm

Printed by Enid Galliers  
**Electronic Mail Message**

Date: 04-Oct-1999 10:47am  
From: Ross Lobell  
ross.lobell@secure.aa.WL.com

Dept:  
Tel No:

TO: Enid Galliers ( galliers@A1 )

Subject: NDA 21-102; Response to Questions

Dear Ms. Galliers:

Attached to this secure E mail are our responses to the 3 questions posed last week. The file is presented in WORD.

I also received your transmission of Division's comments regarding the osteoporosis portion of the label. We will be having a telephone meeting with DRUDP this coming Friday. Will you be participating as well?

<<Galliers ltr104.doc>>

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following annotations on 10/04/99 10:45:53

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[X] Access Manager:

This message was sent by Parke-Davis across the Internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

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FDA questions are followed by Parke-Davis responses.

1. Is there any age matched information, especially for 30 year age bracket which can be used as a baseline CT scan comparison for the data?

An age-standardized population was not available at the time this study was initiated or at study completion. An important reference with regard to QCT is a chapter called *Quantitative Computed Tomography* in a publication called *Primer on Osteoporosis* by Harry K. Genant, Jon E. Block, Bruce Ettinger, Claus-Christian Gluer, and Peter W. Steiger. It represents the state of the CT art at the time that Parke-Davis started osteoporosis trials.

Another reference (Steiger, P., Block, J.E., Steiger, S., Heuck, A.F., Friedlander, A., Ettinger, G., Harris, S.T., Gluer, C.C., Genant, H.K., *Spinal Bone Mineral Density Measured with Quantitative CT: Effect of Region of Interest, Vertebral Level and Technique*. Radiology, 1990, 175:537-543) suggests z-scores, but it is based on data from a single site using a single machine. In the 376-359 study, multiple scanners and calibration phantoms were used and information not obtained on various populations. Thus, only the most expert of radiologists are able to generate normative data for comparison to different populations.

2. Provide a table similar to that on page 48 of the report for % responding patients at 12 and 24 months for the intent-to-treat population.

See attached tables for 12 month and 24 month data for Intent-To-Treat Patients for protocol 376-359 (last page of this submission).

3. Provide baseline characteristics for entire population, regardless of treatment group.

See attached table for baseline patient characteristics for all treatment groups.

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Protocol 376-359  
Baseline Patient Characteristics  
All Intent-to-Treat Patients

|                                    | NA/EE Treatment Group, mg/μg |              |              |              |               | EE Treatment Group, μg |              |               |              |               | Overall             | p-value |
|------------------------------------|------------------------------|--------------|--------------|--------------|---------------|------------------------|--------------|---------------|--------------|---------------|---------------------|---------|
|                                    | Placebo                      | 1/10         |              |              |               | 1                      | 10           |               |              |               |                     |         |
|                                    |                              | 0.2/1        | 0.5/2.5      | 1/5          | 1/10          |                        | 2.5          | 5             | 10           |               |                     |         |
| N                                  | 123                          | 119          | 120          | 124          | 118           | 119                    | 120          | 121           | 101          | 1065          |                     |         |
| Age                                |                              |              |              |              |               |                        |              |               |              |               | 0.9627 <sup>a</sup> |         |
| Mean (SD)                          | 51.7 (4.1)                   | 52.2 (3.8)   | 51.9 (4.2)   | 51.9 (3.7)   | 52.2 (3.8)    | 52.5 (4.1)             | 51.8 (4.1)   | 51.9 (3.8)    | 51.8 (4.3)   | 52.0 (4.0)    |                     |         |
| Median (min, max)                  | 52 (41, 62)                  | 52 (40, 64)  | 53 (40, 60)  | 52 (42, 59)  | 52 (40, 62)   | 53 (42, 63)            | 52 (40, 61)  | 52 (40, 61)   | 52 (40, 62)  | 52 (40, 64)   |                     |         |
| Months Since Last Menstrual Period |                              |              |              |              |               |                        |              |               |              |               | 0.1410 <sup>a</sup> |         |
| Mean (SD)                          | 31.6 (17.2)                  | 33.4 (16.3)  | 32.7 (15.8)  | 31.2 (16.8)  | 30.5 (19.7)   | 31.5 (16.6)            | 28.2 (17.9)  | 32.5 (18.4)   | 29.7 (17.2)  | 31.3 (17.3)   |                     |         |
| Median (min, max)                  | 32.0 (2, 66)                 | 33.0 (4, 61) | 31.5 (7, 62) | 31.0 (5, 60) | 26.0 (4, 116) | 32.0 (1, 60)           | 24.0 (2, 70) | 33.0 (1, 108) | 28.0 (5, 67) | 30.0 (1, 116) |                     |         |
| Race, n (%)                        |                              |              |              |              |               |                        |              |               |              |               | 0.560 <sup>b</sup>  |         |
| White                              | 119 (97)                     | 111 (93)     | 112 (93)     | 117 (94)     | 115 (98)      | 115 (97)               | 115 (96)     | 116 (96)      | 98 (97)      | 1018 (96)     |                     |         |
| Black                              | 2 (2)                        | 0 (0)        | 3 (3)        | 2 (2)        | 0 (0)         | 2 (2)                  | 1 (1)        | 2 (2)         | 0 (0)        | 12 (1)        |                     |         |
| Other                              | 2 (2)                        | 8 (7)        | 5 (4)        | 5 (4)        | 3 (3)         | 2 (2)                  | 4 (3)        | 3 (3)         | 3 (3)        | 35 (3)        |                     |         |
| Physically Active, n (%)           |                              |              |              |              |               |                        |              |               |              |               | 0.102 <sup>b</sup>  |         |
| Yes                                | 80 (65)                      | 82 (69)      | 76 (63)      | 86 (69)      | 74 (63)       | 71 (60)                | 69 (58)      | 69 (57)       | 75 (74)      | 682 (64)      |                     |         |
| No                                 | 43 (35)                      | 37 (31)      | 44 (37)      | 38 (31)      | 44 (37)       | 48 (40)                | 51 (43)      | 52 (43)       | 26 (26)      | 383 (36)      |                     |         |
| Smoking History, n (%)             |                              |              |              |              |               |                        |              |               |              |               | 0.210 <sup>b</sup>  |         |
| Never                              | 55 (45)                      | 58 (49)      | 53 (44)      | 66 (53)      | 51 (43)       | 58 (49)                | 52 (43)      | 57 (47)       | 44 (44)      | 494 (46)      |                     |         |
| Stopped                            | 37 (30)                      | 30 (25)      | 36 (30)      | 30 (24)      | 35 (30)       | 45 (38)                | 40 (33)      | 38 (31)       | 26 (26)      | 317 (30)      |                     |         |
| Light                              | 8 (7)                        | 13 (11)      | 8 (7)        | 10 (8)       | 5 (4)         | 5 (4)                  | 11 (9)       | 7 (6)         | 10 (10)      | 77 (7)        |                     |         |
| Moderate                           | 20 (16)                      | 15 (13)      | 14 (12)      | 15 (12)      | 17 (14)       | 7 (6)                  | 13 (11)      | 10 (8)        | 17 (17)      | 128 (12)      |                     |         |
| Heavy                              | 3 (2)                        | 3 (3)        | 9 (8)        | 3 (2)        | 10 (9)        | 4 (3)                  | 4 (3)        | 9 (7)         | 4 (4)        | 49 (5)        |                     |         |

<sup>a</sup> From Analysis of Variance  
<sup>b</sup> From Chi-Square test

Protocol 376-359  
Baseline Patient Characteristics  
All Intent-to-Treat Patients (Cont.)

|                                 | NA/EE Treatment Group, mg/μg |            |            |            |            | EE Treatment Group, μg |            |            |            | Overall    | p-value             |
|---------------------------------|------------------------------|------------|------------|------------|------------|------------------------|------------|------------|------------|------------|---------------------|
|                                 | Placebo                      | 0.2/1      | 0.5/2.5    | 1/5        | 1/10       | 1                      | 2.5        | 5          | 10         |            |                     |
| N                               | 123                          | 119        | 120        | 124        | 118        | 119                    | 120        | 121        | 101        | 1065       |                     |
| Systolic Blood Pressure, mm Hg  |                              |            |            |            |            |                        |            |            |            |            |                     |
| Mean (SD)                       | 119 (12.9)                   | 121 (15.2) | 121 (17.2) | 118 (13.1) | 122 (15.0) | 121 (15.2)             | 119 (13.0) | 119 (14.2) | 118 (12.4) | 120 (14.3) | 0.2155 <sup>a</sup> |
| Diastolic Blood Pressure, mm Hg |                              |            |            |            |            |                        |            |            |            |            |                     |
| Mean (SD)                       | 76 (8.3)                     | 77 (8.1)   | 76 (8.9)   | 75 (8.5)   | 76 (7.9)   | 76 (9.1)               | 76 (8.5)   | 76 (8.8)   | 75 (8.6)   | 76 (8.5)   | 0.6614 <sup>a</sup> |
| Weight, kg                      |                              |            |            |            |            |                        |            |            |            |            |                     |
| Mean (SD)                       | 64 (9.2)                     | 65 (9.1)   | 66 (9.5)   | 64 (8.7)   | 65 (9.4)   | 67 (8.8)               | 65 (9.4)   | 65 (9.3)   | 66 (9.0)   | 65 (9.2)   | 0.1183 <sup>a</sup> |
| Height, cm                      |                              |            |            |            |            |                        |            |            |            |            |                     |
| Mean (SD)                       | 164 (7.2)                    | 164 (5.8)  | 164 (6.1)  | 163 (7.4)  | 164 (6.3)  | 165 (5.9)              | 164 (5.9)  | 164 (6.9)  | 163 (11.0) | 164 (7.1)  | 0.5347 <sup>a</sup> |

<sup>a</sup> From Analysis of Variance

<sup>b</sup> From Chi-Square test

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Protocol 376-359  
 Percentage of Patients Responding to Therapy (No Decrease from Baseline in BMD)  
 Months 12 and 24  
 All Intent-to-Treat Patients

|                    |  | NA/EE Treatment Group, mg/ $\mu$ g |       |         |     |      | EE Treatment Group, $\mu$ g |     |     |     |  |
|--------------------|--|------------------------------------|-------|---------|-----|------|-----------------------------|-----|-----|-----|--|
|                    |  | Placebo                            | 0.2/1 | 0.5/2.5 | 1/5 | 1/10 | 1                           | 2.5 | 5   | 10  |  |
|                    |  |                                    |       |         |     |      |                             |     |     |     |  |
| Month 12           |  |                                    |       |         |     |      |                             |     |     |     |  |
| N                  |  | 112                                | 109   | 115     | 117 | 112  | 115                         | 118 | 117 | 99  |  |
| Percent Responding |  | 35                                 | 37    | 47      | 69  | 73   | 50                          | 43  | 50  | 64  |  |
| Month 24           |  |                                    |       |         |     |      |                             |     |     |     |  |
| N                  |  | 123                                | 119   | 120     | 124 | 118  | 119                         | 120 | 121 | 101 |  |
| Percent Responding |  | 24                                 | 39    | 39      | 56  | 66   | 36                          | 38  | 36  | 62  |  |

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Printed by Enid Galliers  
**Electronic Mail Message**

**Date:** 01-Oct-1999 01:03pm  
**From:** Joanna Zawadzki  
ZAWADZKIJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6430 FAX 301-443-9282

**Subject:** Labeling Recommendations

Enid,

Attached are the revised labeling recommendations.

Joanna

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**Labeling Recommendations** – Division of Metabolic and Endocrine Drug Products  
9/27/99 – Revised 9/30/99 after withdrawal of [REDACTED]

Specific recommendations for the physician label for norethindrone acetate/ethinyl estradiol regarding the osteoporosis indication are listed below. In addition, several recommendations regarding nomenclature are also made. Page numbers refer to page numbers in the physician package insert, as submitted in Volume 1 of the NDA. We have just received a copy of the currently updated label forwarded by the sponsor to the Division of Reproductive and Urologic Drug Products and we will be discussing additional changes with them internally.

| CHANGE                                                                                                                                                                                                                                                                                                                                                                                                      | REASON                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Page 13 of 32:</p> <p>Delete [REDACTED]</p>                                                                                                                                                                                                                                                                                                                                                              | <p>Reference to the name [REDACTED] has been removed from the label by HFD-580. An acronym in the label may confuse the clinician. A more specific description of the studied population provides the clinician with a clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug.</p>                                                                                                                                                                                                                                                                                                                                                                                         |
| <p>Page 13 of 32:</p> <p>Insert "A total of 283 postmenopausal women with intact uteri and normal baseline bone mineral density ( [REDACTED] mg/cc) were randomized to FemHRT 1/5 mg norethindrone acetate/mcg ethinyl estradiol [REDACTED] placebo, and 87% contributed data to the Intent-To-Treat analysis. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented."</p> | <p>A more specific description of the studied population provides the clinician with a clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug.</p> <p><i>Comments to sponsor:</i></p> <p>(1) Please supply the correct baseline BMD for this randomized population ( 1/5 (mg norethindrone acetate/mcg ethinyl estradiol) dose and placebo).</p> <p>(2) [REDACTED]</p> <p>(3) [REDACTED]</p> <p>(4) Please print in bold "mg" and "mcg" to minimize confusion about the dosages of norethindrone acetate/ ethinyl estradiol</p> <p>(5) The low supplementation with calcium and absence of vitamin D supplementation may partially explain the BMD loss in the placebo</p> |

|                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                           | group.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p>Page 13 of 32:</p> <p><i>Insert</i><br/> “(mg norethindrone acetate/mcg ethinyl estradiol)” [redacted]</p>                                                                                                                                                                                             | <p>The inclusion of this description minimizes confusion about the relative contributions of the progestogen and estrogen in this combination.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <p>Page 14 of 32:</p> <p><i>Delete</i> [redacted]</p>                                                                                                                                                                                                                                                     | <ol style="list-style-type: none"> <li>(1) The original protocol was designed to compare the BMD of each treatment group to placebo. The original protocol was not designed to account for multiple comparisons of different treatment groups.</li> <li>(2) The [redacted] are not mentioned in this section.</li> <li>(3) Including this reference is confusing to the clinician, particularly since [redacted]</li> </ol>                                                                                                                                                                                                                              |
| <p>Page 14 of 32:</p> <p><i>Please note the following inserted comment:</i></p> <p>[Note to sponsor: Please change ordinate label to “Percent Change in Lumbar Spine Bone Mineral Density from Baseline (+SE)” and change table accordingly. [redacted] [redacted] should be removed from the table.]</p> | <ol style="list-style-type: none"> <li>(1) Quantitative computerized tomography is often used in research studies, but less commonly used in clinical practice. Clinicians may not be familiar with the units.</li> <li>(2) Other labels for drugs with the osteoporosis indication depict “percent change.” We understand that the sponsor’s primary efficacy for BMD was change in BMD and not percent change in BMD. However, we are trying to maintain consistency across labels to simplify the message for the practicing clinician.</li> <li>(3) Inclusion of doses not approved for osteoporosis would be confusing to the clinician.</li> </ol> |
| <p>Page 14 of 32:</p> <p><i>Please note the following modified figure legend:</i></p> <p>FIGURE 4. Percent Change in Lumbar Spine Bone Mineral Density <math>\pm</math>SE) From Baseline at Month 12 and Month 24</p>                                                                                     | <p>Title of figure should reflect the presented data.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>Page 14 of 32:</p> <p><i>Please note the following inserted comment:</i></p>                                                                                                                                                                                                                           | <p>For consistency in the osteoporosis label, the FDA statisticians have recommended the depiction of the Intent To Treat analysis in the</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>[<i>Note to Sponsor:</i> Data presented should be based on Intent to Treat Analysis with Last Observation Carried Forward.]</p> | <p>label, as this analysis is preferred by the FDA. Please see "E9 Statistical Principles for Clinical Trials", Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98</p> <p>Please also submit a copy of the Intent-to-Treat Analysis at 12 months for FDA review, as it was not included in the NDA.</p>                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p><u>General change:</u><br/>Order of active ingredient presentation as NA/EE.</p>                                                | <p>The Division of Metabolic and Endocrine Drug Products understands that the sponsor has discussed this issue with the Division of Reproductive and Urologic Drug Products. However, we must comment, as we too feel that placing the progestogen before the estrogen has a precedent in a drug marketed for oral contraception but not in a drug marketed for osteoporosis. The change in the order of the estrogen and progestogen, particularly since there is a 1000 fold difference between the estrogen and progesterone dosage strengths though the actual numbers are of the same order of magnitude, could be misleading to the clinician.</p>                                                                |
| <p><u>General change:</u><br/>Change of Proposed Trade Name FemHRT</p>                                                             | <p>The Division of Metabolic and Endocrine Drug Products finds this trade name potentially misleading to the clinician because of the possible implication of "heart" from "HRT".</p> <ol style="list-style-type: none"> <li>(1) Current data regarding the cardiac protective effects of estrogen are still controversial.</li> <li>(2) This NDA was not designed with lipids as a primary efficacy outcome. In general, it is still controversial whether the improvement seen in the lipid profile with estrogen therapy confers a benefit.</li> <li>(3) In addition, the 'HRT' acronym is a common abbreviation for hormonal replacement therapy which may be also potentially misleading to clinicians.</li> </ol> |

2 **Page(s) Redacted**

Draft

Labeling

Printed by Enid Galliers  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL      **Date:** 01-Oct-1999 01:53pm  
**From:** Enid Galliers  
          GALLIERS  
**Dept:** HFD-510                      PKLN 14B04  
**Tel No:** 301-827-6429 FAX 301-443-9282

**TO:** ross.lobell@SECURE.aa.wl.com

**Subject:** Labeling Changes related to osteoporosis

Dear Mr. Lobell:

Changes concerning the osteoporosis sections of the labeling for NDA 21-102/NDA 21-065 are attached.

In addition, Dr. Zawadzki would like to know if you have data on beginning and ending heights of study participants.

Finally, do you have an estimate of the time frame for responding to the questions we asked you on September 29?

We received your communication withdrawing

I am using secure email to send this because Dr. Zawadzki and I have now been given access to the secure server.

Thank you,

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products, ODE II, CDER  
Phone: 301-827-6429  
FAX: 301-443-9282

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Printed by Enid Galliers  
**Electronic Mail Message**

**Date:** 01-Oct-1999 06:05pm  
**From:** Ross Lobell  
ross.lobell@secure.aa.WL.com  
**Dept:**  
**Tel No:**

**TO:** Enid Galliers ( galliers@A1 )

**Subject:** NDA 21-102, FemHRT

Dear Ms. Galliers,

Just wanted to let you know that we are nearly finished with the response to the additional questions posed on Sept. 29. The delay is due to receipt of additional questions regarding the vasomotor indication. The responses will be provided to you on Monday, Oct. 4 via secure e-mail.

Thanks for your understanding

Ross Lobell  
Sr. Manager, Worldwide Regulatory Affairs  
Ph. 734-622-111  
FAX 734-622-32283

"WorldSecure Server <secure.cder.fda.gov>" made the following annotations on 10/01/99 18:04:06

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[ - Access Manager:  
ssage was sent by Parke-Davis across the Internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

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**(E-DAVIS)**

September 30, 1999

NDA 21-102  
Ref. No. 002  
FemHRT



Solomon Sobel, M.D.  
Director  
Division of Metabolism and Endocrine  
Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Attention: Document Control Room 14B-04  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to NDA 21-102 for FemHRT and to a fax sent by Ms. Enid Galliers on September 24, 1999. That fax contained 7 questions relating to study 376-359.

Enclosed is our response to each question.

Please note that these responses were also provided by secure E-mail on September 29, 1999 to Ms. Galliers and to Ms. Spell-LeSane (DRUDP).

Should you have any questions regarding this submission please call Mr. Ross Lobell at 734/622-2111 or send a facsimile to 734/622-3283.

Sincerely,

Ross Lobell  
Senior Manager  
Worldwide Regulatory Affairs

RL:kb

09-30-1999\RN-002\21-102\CI-0376\Letter

Attachments

10/13/99  
Data presented here  
was faxed 9/30/99  
and reviewed

/S/

|                                 |                                                               |
|---------------------------------|---------------------------------------------------------------|
| REVIEWS COMPLETED               |                                                               |
| CSO ACTION:                     |                                                               |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS                    | DATE                                                          |

Printed by Enid Galliers  
**Electronic Mail Message**

/S/

Date: 29-Sep-1999 02:37pm  
From: Ross Lobell  
ross.lobell@secure.aa.WL.com

Dept:  
Tel No:

TO: 'GALLIERS@SECURE.CDER.FDA.GOV' ( GALLIERS@A1 )  
TO: 'SPELLLESANED@SECURE.CDER.FDA.GOV' ( SPELLLESANED@A1 )

Subject: NDA 21-102 FemHRT/Osteoporosis Indication

Dear Ms. Galliers and Ms. Spell-LeSane:

Attached is our response to Ms. Galliers September 24 fax which contained 7 questions relating to study 376-359. The response is an attached file and was created in WORD.

Please confirm receipt of this secure E-mail. A hard copy of this response, along with a cover letter will be provided as well.

<<response to 924 fax.doc>>

Ross Lobell  
Senior Manager,  
Worldwide Regulatory Affairs  
Phone: 734 622-2111  
Fax: 734 622-3283  
email: ross.lobell@wl.com

7 cure Server <secure.cder.fda.gov>" made the following  
a: ons on 09/29/99 14:37:33

[INFO] - Access Manager:

This message was sent by Parke-Davis across the internet in encrypted format across the CDER mail VPN and successfully decrypted at CDER.

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Please provide the following clarifications regarding NDA 21-102 (FemHRT), referring to Study 376-359:

- 1) Is quantitative computerized tomography method in Study 376-359 single energy or dual energy?

This study was conducted using the technology available at the time (1988). The method used therefore, was QCT. Single or dual energy parameters relate only to the more recently developed  method and have no relevance to the method used in this trial.

- 2) Patient Disposition – Table 10, Study 376-359

Please clarify definition of completed study, as n for completed study differs from n for the completion of 24 months.

On Table 10, the definition of "24 Months of Treatment Completed" is that a patient received drug for at least  $24 \times 30 = 720$  days. The row "Completed Study" is taken from the end-of-treatment status form completed by the investigator, who may have considered a patient "completed" as long as the patient completed all necessary end-of-study procedures (BMD, lab testing, etc.) even though she may not have received exactly 720 days of study medication.

- 3) Intent-To-Treat Analysis – Please clarify corrected data vs. uncorrected form 5  
What is Form 5 data?

Form 5 data is simply the term used to refer to the uncorrected data. Uncorrected data are those data which could not be corrected across investigational sites. Corrected data were those data available for standardization across all study sites and were equated to a standard site, which, for this study, was

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**4) Please indicate where in the NDA the following data can be found:**

**Table of Baseline Patient Characteristics (similar in design to Table 13 – Patient Characteristics for Evaluable Patients) for all randomized patients, with p-values for across groups comparisons**

**Table of Patient Characteristics (similar in design to Table 13 – Patient Characteristics for Evaluable Patients) for all randomized patients who contribute to Intent-To-Treat analysis, with p-values for across groups comparisons**

The requested tables are presented below:

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Protocol 376-359

Baseline Patient Characteristics

All Randomized Patients

|                                    | NA/EE Treatment Group, mg/μg |              |              |              |               | EE Treatment Group, μg |               |               |              | p-value             |
|------------------------------------|------------------------------|--------------|--------------|--------------|---------------|------------------------|---------------|---------------|--------------|---------------------|
|                                    | Placebo                      | 0.2/1        | 0.5/2.5      | 1/5          | 1/10          | 1                      | 2.5           | 5             | 10           |                     |
| N                                  | 137                          | 139          | 136          | 146          | 145           | 141                    | 137           | 141           | 143          |                     |
| Age                                |                              |              |              |              |               |                        |               |               |              | 0.9627 <sup>a</sup> |
| Mean (SD)                          | 51.7 (4.1)                   | 52.5 (3.9)   | 51.8 (4.2)   | 51.6 (4.0)   | 52.1 (3.6)    | 52.2 (4.1)             | 51.8 (4.2)    | 52.0 (4.0)    | 51.9 (4.4)   |                     |
| Median (min, max)                  | 52 (41, 62)                  | 52 (40, 64)  | 53 (40, 60)  | 52 (42, 63)  | 52 (40, 62)   | 53 (40, 63)            | 52 (40, 62)   | 52 (40, 63)   | 52 (40, 62)  |                     |
| Months Since Last Menstrual Period |                              |              |              |              |               |                        |               |               |              | 0.1740 <sup>a</sup> |
| Mean (SD)                          | 31.5 (20.2)                  | 33.1 (16.0)  | 32.3 (16.5)  | 31.2 (17.3)  | 30.7 (18.9)   | 31.8 (16.5)            | 29.2 (19.5)   | 32.8 (19.4)   | 29.1 (17.2)  |                     |
| Median (min, max)                  | 31.0 (2, 154)                | 32.0 (4, 61) | 31.0 (6, 68) | 30.5 (1, 79) | 29.0 (4, 116) | 33.0 (1, 60)           | 24.5 (2, 122) | 32.0 (1, 108) | 27.0 (4, 67) |                     |
| Race, n (%)                        |                              |              |              |              |               |                        |               |               |              | 0.771 <sup>b</sup>  |
| White                              | 131 (96)                     | 129 (93)     | 128 (94)     | 135 (93)     | 141 (97)      | 134 (95)               | 132 (96)      | 135 (96)      | 137 (96)     |                     |
| Black                              | 2 (2)                        | 1 (1)        | 3 (2)        | 2 (1)        | 0 (0)         | 3 (2)                  | 1 (1)         | 2 (1)         | 2 (1)        |                     |
| Other                              | 4 (3)                        | 9 (7)        | 5 (4)        | 9 (6)        | 4 (3)         | 4 (3)                  | 4 (3)         | 4 (3)         | 4 (3)        |                     |
| Physically Active, n (%)           |                              |              |              |              |               |                        |               |               |              | 0.585 <sup>b</sup>  |
| Yes                                | 87 (64)                      | 92 (66)      | 85 (62)      | 98 (67)      | 86 (59)       | 86 (61)                | 79 (58)       | 84 (60)       | 97 (68)      |                     |
| No                                 | 50 (36)                      | 47 (34)      | 51 (38)      | 48 (33)      | 59 (41)       | 55 (39)                | 58 (42)       | 57 (40)       | 46 (32)      |                     |
| Smoking History, n (%)             |                              |              |              |              |               |                        |               |               |              | 0.554 <sup>b</sup>  |
| Never                              | 62 (45)                      | 68 (49)      | 59 (43)      | 72 (49)      | 61 (42)       | 64 (45)                | 59 (43)       | 64 (45)       | 59 (41)      |                     |
| Stopped                            | 41 (30)                      | 35 (25)      | 43 (32)      | 36 (25)      | 48 (33)       | 54 (38)                | 45 (33)       | 45 (32)       | 43 (30)      |                     |
| Light                              | 9 (7)                        | 14 (10)      | 8 (6)        | 12 (8)       | 7 (5)         | 8 (6)                  | 11 (8)        | 10 (7)        | 14 (10)      |                     |
| Moderate                           | 22 (16)                      | 17 (12)      | 16 (12)      | 21 (14)      | 18 (12)       | 10 (7)                 | 18 (13)       | 13 (9)        | 21 (15)      |                     |
| Heavy                              | 3 (2)                        | 5 (4)        | 10 (7)       | 5 (3)        | 11 (8)        | 5 (4)                  | 4 (3)         | 9 (6)         | 6 (4)        |                     |

<sup>a</sup> From Analysis of Variance<sup>b</sup> From Chi-Square testAPPEARS THIS WAY  
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Protocol 376-359  
Baseline Patient Characteristics  
All Randomized Patients (Cont.)

|                                 | NA/EE Treatment Group, mg/μg |            |            |            |            | EE Treatment Group, μg |            |            |            | p-value  |
|---------------------------------|------------------------------|------------|------------|------------|------------|------------------------|------------|------------|------------|----------|
|                                 | Placebo                      | 0.2/1      | 0.5/2.5    | 1/5        | 1/10       | 1                      | 2.5        | 5          | 10         |          |
| N                               | 137                          | 139        | 136        | 146        | 145        | 141                    | 137        | 141        | 143        |          |
| Systolic Blood Pressure, mm Hg  |                              |            |            |            |            |                        |            |            |            |          |
| Mean (SD)                       | 119 (12.8)                   | 122 (15.1) | 120 (16.5) | 118 (13.4) | 122 (14.9) | 120 (14.8)             | 119 (13.2) | 119 (14.2) | 119 (12.6) | 0.3649 * |
| Diastolic Blood Pressure, mm Hg |                              |            |            |            |            |                        |            |            |            |          |
| Mean (SD)                       | 75 (8.6)                     | 77 (8.2)   | 75 (8.7)   | 75 (8.6)   | 76 (7.9)   | 76 (8.7)               | 76 (8.4)   | 76 (8.6)   | 75 (8.8)   | 0.9892 * |
| Weight, kg                      |                              |            |            |            |            |                        |            |            |            |          |
| Mean (SD)                       | 63 (9.2)                     | 65 (9.3)   | 66 (9.4)   | 64 (8.9)   | 65 (9.7)   | 66 (8.8)               | 65 (9.2)   | 65 (9.5)   | 66 (9.1)   | 0.1404 * |
| Height, cm                      |                              |            |            |            |            |                        |            |            |            |          |
| Mean (SD)                       | 163 (7.1)                    | 165 (5.7)  | 164 (6.0)  | 163 (7.1)  | 164 (6.4)  | 165 (5.8)              | 164 (6.7)  | 164 (6.7)  | 163 (10.5) | 0.5336 * |

\* From Analysis of Variance

† From Chi-Square test

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Protocol 376-359

Baseline Patient Characteristics  
All Intent-to-Treat Patients

|                                    | Placebo<br>N | NA/EE Treatment Group, mg/μg |              |              |               |              | EE Treatment Group, μg |               |              |                     |  | p-value |
|------------------------------------|--------------|------------------------------|--------------|--------------|---------------|--------------|------------------------|---------------|--------------|---------------------|--|---------|
|                                    |              | 0.2/1                        | 0.5/2.5      | 1/5          | 1/10          | 1            | 2.5                    | 5             | 10           |                     |  |         |
| Age                                | 123          | 119                          | 120          | 124          | 118           | 119          | 120                    | 121           | 101          |                     |  |         |
| Mean (SD)                          | 51.7 (4.1)   | 52.2 (3.8)                   | 51.9 (4.2)   | 51.9 (3.7)   | 52.2 (3.8)    | 52.5 (4.1)   | 51.8 (4.1)             | 51.9 (3.8)    | 51.8 (4.3)   | 0.9627 <sup>a</sup> |  |         |
| Median (min, max)                  | 52 (41, 62)  | 52 (40, 64)                  | 53 (40, 60)  | 52 (42, 59)  | 52 (40, 62)   | 53 (42, 63)  | 52 (40, 61)            | 52 (40, 61)   | 52 (40, 62)  |                     |  |         |
| Months Since Last Menstrual Period |              |                              |              |              |               |              |                        |               |              |                     |  |         |
| Mean (SD)                          | 31.6 (17.2)  | 33.4 (16.3)                  | 32.7 (15.8)  | 31.2 (16.8)  | 30.5 (19.7)   | 31.5 (16.6)  | 28.2 (17.9)            | 32.5 (18.4)   | 29.7 (17.2)  | 0.1410 <sup>a</sup> |  |         |
| Median (min, max)                  | 32.0 (2, 66) | 33.0 (4, 61)                 | 31.5 (7, 62) | 31.0 (5, 60) | 26.0 (4, 116) | 32.0 (1, 60) | 24.0 (2, 70)           | 33.0 (1, 108) | 28.0 (5, 67) |                     |  |         |
| Race, n (%)                        |              |                              |              |              |               |              |                        |               |              | 0.560 <sup>b</sup>  |  |         |
| White                              | 119 (97)     | 111 (93)                     | 112 (93)     | 117 (94)     | 115 (98)      | 115 (97)     | 115 (96)               | 116 (96)      | 98 (97)      |                     |  |         |
| Black                              | 2 (2)        | 0 (0)                        | 3 (3)        | 2 (2)        | 0 (0)         | 2 (2)        | 1 (1)                  | 2 (2)         | 0 (0)        |                     |  |         |
| Other                              | 2 (2)        | 8 (7)                        | 5 (4)        | 5 (4)        | 3 (3)         | 2 (2)        | 4 (3)                  | 3 (3)         | 3 (3)        |                     |  |         |
| Physically Active, n (%)           |              |                              |              |              |               |              |                        |               |              | 0.102 <sup>b</sup>  |  |         |
| Yes                                | 80 (65)      | 82 (69)                      | 76 (63)      | 86 (69)      | 74 (63)       | 71 (60)      | 69 (58)                | 69 (57)       | 75 (74)      |                     |  |         |
| No                                 | 43 (35)      | 37 (31)                      | 44 (37)      | 38 (31)      | 44 (37)       | 48 (40)      | 51 (43)                | 52 (43)       | 26 (26)      |                     |  |         |
| Smoking History, n (%)             |              |                              |              |              |               |              |                        |               |              | 0.210 <sup>b</sup>  |  |         |
| Never                              | 55 (45)      | 58 (49)                      | 53 (44)      | 66 (53)      | 51 (43)       | 58 (49)      | 52 (43)                | 57 (47)       | 44 (44)      |                     |  |         |
| Stopped                            | 37 (30)      | 30 (25)                      | 36 (30)      | 30 (24)      | 35 (30)       | 45 (38)      | 40 (33)                | 38 (31)       | 26 (26)      |                     |  |         |
| Light                              | 8 (7)        | 13 (11)                      | 8 (7)        | 10 (8)       | 5 (4)         | 5 (4)        | 11 (9)                 | 7 (6)         | 10 (10)      |                     |  |         |
| Moderate                           | 20 (16)      | 15 (13)                      | 14 (12)      | 15 (12)      | 17 (14)       | 7 (6)        | 13 (11)                | 10 (8)        | 17 (17)      |                     |  |         |
| Heavy                              | 3 (2)        | 3 (3)                        | 9 (8)        | 3 (2)        | 10 (9)        | 4 (3)        | 4 (3)                  | 9 (7)         | 4 (4)        |                     |  |         |

<sup>a</sup> From Analysis of Variance

<sup>b</sup> From Chi-Square test

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Protocol 376-359  
Baseline Patient Characteristics  
All Intent-to-Treat Patients (Cont.)

|                                 | NA/EE Treatment Group, mg/μg |            |            |            | EE Treatment Group, μg |            |            |            | p-value    |
|---------------------------------|------------------------------|------------|------------|------------|------------------------|------------|------------|------------|------------|
|                                 | Placebo                      | 0.2/1      | 0.5/2.5    | 1/5        | 1/10                   | 1          | 2.5        | 5          |            |
| N                               | 123                          | 119        | 120        | 124        | 118                    | 119        | 120        | 121        | 101        |
| Systolic Blood Pressure, mm Hg  |                              |            |            |            |                        |            |            |            |            |
| Mean (SD)                       | 119 (12.9)                   | 121 (15.2) | 121 (17.2) | 118 (13.1) | 122 (15.0)             | 121 (15.2) | 119 (13.0) | 119 (14.2) | 118 (12.4) |
| Diastolic Blood Pressure, mm Hg |                              |            |            |            |                        |            |            |            |            |
| Mean (SD)                       | 76 (8.3)                     | 77 (8.1)   | 76 (8.9)   | 75 (8.5)   | 76 (7.9)               | 76 (9.1)   | 76 (8.5)   | 76 (8.8)   | 75 (8.6)   |
| Weight, kg                      |                              |            |            |            |                        |            |            |            |            |
| Mean (SD)                       | 64 (9.2)                     | 65 (9.1)   | 66 (9.5)   | 64 (8.7)   | 65 (9.4)               | 67 (8.8)   | 65 (9.4)   | 65 (9.3)   | 66 (9.0)   |
| Height, cm                      |                              |            |            |            |                        |            |            |            |            |
| Mean (SD)                       | 164 (7.2)                    | 164 (5.8)  | 164 (6.1)  | 163 (7.4)  | 164 (6.3)              | 165 (5.9)  | 164 (5.9)  | 164 (6.9)  | 163 (11.6) |

\* From Analysis of Variance

† From Chi-Square test

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- 5) Tables comparable to Table Appendix C-4, Table 17, Table Appendix C-5, Table 14 for Intent-To-Treat, Observed Cases, and Evaluable Analyses with p-values for percent change from baseline:

p-value (NA/EE or EE vs. placebo)

p-value (Follow up vs. Baseline)

95% Confidence Interval (NA/EE or EE vs. Placebo)

p-value (NA/EE vs. EE)

The requested tables are presented below:

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Protocol 376-359

Percent Change from Baseline in Bone Mineral Density

ITT Data: Corrected & Uncorrected

Reference: Appendix C.4

| Month 24                                                          | Placebo | NA/EE Treatment Group, mg/ $\mu$ g |                  |                  |                  | EE Treatment Group, $\mu$ g |                  |                  |                  |  |
|-------------------------------------------------------------------|---------|------------------------------------|------------------|------------------|------------------|-----------------------------|------------------|------------------|------------------|--|
|                                                                   |         | 0.2/1                              | 0.5/2.5          | 1/5              | 1/10             | 1                           | 2.5              | 5                | 10               |  |
|                                                                   |         |                                    |                  |                  |                  |                             |                  |                  |                  |  |
| N                                                                 | 123     | 119                                | 120              | 124              | 118              | 119                         | 120              | 121              | 101              |  |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.0198                             | 0.0008           | 0.0001           | 0.0001           | 0.0150                      | 0.0202           | 0.0010           | 0.0001           |  |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [0.5, $\infty$ ]                   | [2.0, $\infty$ ] | [5.7, $\infty$ ] | [7.4, $\infty$ ] | [0.7, $\infty$ ]            | [0.5, $\infty$ ] | [2.0, $\infty$ ] | [5.2, $\infty$ ] |  |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0001  | 0.4647                             | 0.5355           | 0.0001           | 0.0001           | 0.5585                      | 0.4545           | 0.5827           | 0.0007           |  |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.9150                             | 0.3209           | 0.0109           | 0.2041           | --                          | --               | --               | --               |  |

<sup>a</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is  $\leq$  to the mean change in the placebo group.

<sup>b</sup> For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

<sup>c</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>d</sup> The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

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Protocol 376-359

Percent Change from Baseline in Bone Mineral Density

ITT Data: Uncorrected Form 5 Data

Reference: Table 17

| Month 24                                                          | Placebo | NA/EE Treatment Group, mg/ $\mu$ g |                  |                  |                  | EE Treatment Group, $\mu$ g |                  |                  |                  |
|-------------------------------------------------------------------|---------|------------------------------------|------------------|------------------|------------------|-----------------------------|------------------|------------------|------------------|
|                                                                   |         | 0.2/1                              | 0.5/2.5          | 1/5              | 1/10             | 1                           | 2.5              | 5                | 10               |
|                                                                   |         |                                    |                  |                  |                  |                             |                  |                  |                  |
| N                                                                 | 123     | 119                                | 120              | 124              | 118              | 119                         | 120              | 121              | 100              |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.0071                             | 0.0039           | 0.0001           | 0.0001           | 0.1550                      | 0.0166           | 0.0100           | 0.0001           |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [1.0, $\infty$ ]                   | [1.2, $\infty$ ] | [6.1, $\infty$ ] | [7.4, $\infty$ ] | [-0.7, $\infty$ ]           | [0.6, $\infty$ ] | [0.8, $\infty$ ] | [5.2, $\infty$ ] |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0001  | 0.8700                             | 0.6762           | 0.0001           | 0.0001           | 0.1170                      | 0.8140           | 0.9986           | 0.0001           |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.2060                             | 0.6352           | 0.0001           | 0.1349           | --                          | --               | --               | --               |

<sup>a</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is  $\leq$  to the mean change in the placebo group.

<sup>b</sup> For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

<sup>c</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>d</sup> The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

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Protocol 376-359

Percent Change from Baseline in Bone Mineral Density  
Evaluable Data

Reference: Table 14

|                                                                   | Placebo | NA/EE Treatment Group, mg/ $\mu$ g |                  |                  |                  | EE Treatment Group, $\mu$ g |                   |                  |                   |
|-------------------------------------------------------------------|---------|------------------------------------|------------------|------------------|------------------|-----------------------------|-------------------|------------------|-------------------|
|                                                                   |         | 0.2/1                              | 0.5/2.5          | 1/5              | 1/10             | 1                           | 2.5               | 5                | 10                |
| <b>Month 12</b>                                                   |         |                                    |                  |                  |                  |                             |                   |                  |                   |
| N                                                                 | 98      | 94                                 | 93               | 96               | 92               | 92                          | 96                | 99               | 51                |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.3162                             | 0.0019           | 0.0001           | 0.0001           | 0.1976                      | 0.0670            | 0.0424           | 0.0002            |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [-1.4, $\infty$ ]                  | [1.5, $\infty$ ] | [4.3, $\infty$ ] | [5.0, $\infty$ ] | [-0.9, $\infty$ ]           | [-0.2, $\infty$ ] | [0.1, $\infty$ ] | [2.9, $\infty$ ]  |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0019  | 0.1218                             | 0.1946           | 0.0001           | 0.0001           | 0.2765                      | 0.7036            | 0.8975           | 0.0163            |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.7394                             | 0.2061           | 0.0013           | 0.3189           | --                          | --                | --               | --                |
| <b>Month 24</b>                                                   |         |                                    |                  |                  |                  |                             |                   |                  |                   |
| N                                                                 | 86      | 86                                 | 85               | 89               | 88               | 81                          | 80                | 90               | 10                |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.1094                             | 0.0026           | 0.0001           | 0.0001           | 0.0229                      | 0.0449            | 0.0116           | 0.0826            |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [-0.7, $\infty$ ]                  | [1.9, $\infty$ ] | [5.9, $\infty$ ] | [7.1, $\infty$ ] | [0.6, $\infty$ ]            | [0.1, $\infty$ ]  | [1.0, $\infty$ ] | [-0.9, $\infty$ ] |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0002  | 0.1707                             | 0.5889           | 0.0004           | 0.0001           | 0.7280                      | 0.4955            | 0.8925           | 0.4445            |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.4608                             | 0.3621           | 0.0061           | 0.4805           | --                          | --                | --               | --                |

<sup>a</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is  $\leq$  to the mean change in the placebo group.

<sup>b</sup> For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

<sup>c</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>d</sup> The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

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Protocol 376-359

Percent Change from Baseline in Bone Mineral Density

Observed Cases Data

Reference: Appendix C.5

|                                                                   | Placebo | NA/EE Treatment Group, mg/μg |          |          |          |  | EE Treatment Group, μg |           |          |           |  |
|-------------------------------------------------------------------|---------|------------------------------|----------|----------|----------|--|------------------------|-----------|----------|-----------|--|
|                                                                   |         | 0.2/1                        | 0.5/2.5  | 1/5      | 1/10     |  | 1                      | 2.5       | 5        | 10        |  |
| <b>Month 12</b>                                                   |         |                              |          |          |          |  |                        |           |          |           |  |
| N                                                                 | 109     | 105                          | 110      | 111      | 105      |  | 108                    | 111       | 112      | 60        |  |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.2941                       | 0.0025   | 0.0001   | 0.0001   |  | 0.0922                 | 0.0864    | 0.0335   | 0.0001    |  |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [-1.2, ∞]                    | [1.3, ∞] | [4.5, ∞] | [5.2, ∞] |  | [-0.4, ∞]              | [-0.3, ∞] | [0.2, ∞] | [2.8, ∞]  |  |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0055  | 0.2603                       | 0.1194   | 0.0001   | 0.0001   |  | 0.8222                 | 0.8409    | 0.7170   | 0.0057    |  |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.4962                       | 0.1931   | 0.0006   | 0.2123   |  | --                     | --        | --       | --        |  |
| <b>Month 24</b>                                                   |         |                              |          |          |          |  |                        |           |          |           |  |
| N                                                                 | 97      | 99                           | 99       | 102      | 98       |  | 96                     | 92        | 105      | 14        |  |
| p-value <sup>a</sup> (NA/EE or EE vs. Placebo)                    | --      | 0.0643                       | 0.0057   | 0.0001   | 0.0001   |  | 0.0559                 | 0.0473    | 0.0049   | 0.1177    |  |
| 95% Confidence Interval <sup>b</sup><br>(NA/EE or EE vs. Placebo) | --      | [-0.2, ∞]                    | [1.4, ∞] | [6.0, ∞] | [6.9, ∞] |  | [-0.1, ∞]              | [0.0, ∞]  | [1.4, ∞] | [-1.4, ∞] |  |
| p-value <sup>c</sup> (Follow-up vs. Baseline)                     | 0.0019  | 0.6958                       | 0.3964   | 0.0001   | 0.0001   |  | 0.8179                 | 0.9149    | 0.3738   | 0.4798    |  |
| p-value <sup>d</sup> (NA/EE vs EE)                                | --      | 0.9059                       | 0.4866   | 0.0060   | 0.2255   |  | --                     | --        | --       | --        |  |

<sup>a</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.

<sup>b</sup> For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

<sup>c</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>d</sup> The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

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- 6) Please provide mean baseline lumbar spine bone mineral density  $\pm$  SD for all randomized patients and also for all randomized patients who contributed to the Intent-To-Treat Analysis.

The requested data are presented in the tables below:

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Protocol 376-359  
Baseline Lumbar Spine Bone Mineral Density  
All Randomized Patients

|           | NA/EE Treatment Group, mg/ $\mu$ g |        |         |        |        | EE Treatment Group, $\mu$ g |        |        |        |
|-----------|------------------------------------|--------|---------|--------|--------|-----------------------------|--------|--------|--------|
|           | Placebo                            | 0.2/1  | 0.5/2.5 | 1/5    | 1/10   | 1                           | 2.5    | 5      | 10     |
| N         | 136                                | 139    | 136     | 146    | 145    | 140                         | 136    | 141    | 143    |
| Mean      | 124.26                             | 122.91 | 125.37  | 123.07 | 125.10 | 123.58                      | 121.82 | 123.83 | 125.20 |
| SD        | 22.19                              | 18.29  | 21.19   | 17.14  | 19.41  | 18.58                       | 20.61  | 19.90  | 19.08  |
| Mean - SD | 102.07                             | 104.62 | 104.18  | 105.93 | 105.69 | 105.00                      | 101.21 | 103.93 | 106.12 |
| Mean + SD | 146.45                             | 141.20 | 146.56  | 140.21 | 144.51 | 142.16                      | 142.43 | 143.73 | 144.28 |

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Protocol 376-359  
Baseline Lumbar Spine Bone Mineral Density  
All Intent-to-Treat Patients

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|           | Placebo | NA/EE Treatment Group, mg/ $\mu$ g |         |        |        | EE Treatment Group, $\mu$ g |        |        |        |
|-----------|---------|------------------------------------|---------|--------|--------|-----------------------------|--------|--------|--------|
|           |         | 0.2/1                              | 0.5/2.5 | 1/5    | 1/10   | 1                           | 2.5    | 5      | 10     |
| N         | 123     | 119                                | 120     | 124    | 118    | 119                         | 120    | 121    | 101    |
| Mean      | 119.46  | 120.19                             | 119.79  | 117.82 | 119.36 | 119.79                      | 116.88 | 119.07 | 120.23 |
| SD        | 22.51   | 19.50                              | 20.26   | 17.38  | 20.23  | 18.85                       | 17.86  | 19.73  | 19.68  |
| Mean - SD | 96.95   | 100.69                             | 99.53   | 100.44 | 99.13  | 100.94                      | 99.02  | 99.34  | 100.55 |
| Mean + SD | 141.97  | 139.69                             | 140.05  | 135.20 | 139.59 | 138.64                      | 134.74 | 138.80 | 139.91 |

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- 7) Please provide mean  $\pm$  SD T-scores (comparison to younger (30 year old), sex-matched controls) and Z-scores (comparison to age-matched and sex-matched controls) for bone mineral density for all randomized patients and also for all randomized patients who contributed to Intent-To-Treat Analysis, if available.

As mentioned in our response to question 1, a QCT method was used for the bone scans in this trial; therefore, T- and Z-scores could not be done.

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**Electronic Mail Message**

**Date:** 29-Sep-1999 04:10pm  
**From:** Joanna Zawadzki  
ZAWADZKIJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6430 FAX 301-443-9282

**Subject:** Osteoporosis Label Changes

Marianne, Dornette, and Dan,

Attached are our changes in the osteoporosis section, which we would like to forward to the sponsor tomorrow. Let me know if you have any comments before then. We have left the [redacted] in the label for now. We will be discussing the doses further internally, in view of the company's withdrawal of the [redacted] at this time and your concerns regarding the [redacted]

Thanks.

Joanna

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Labeling Recommendations – Division of Metabolic and Endocrine Drug Products  
9/27/99

Specific recommendations for the physician label for norethindrone acetate/ethinyl estradiol regarding the osteoporosis indication are listed below. In addition, several recommendations regarding nomenclature are also made. Page numbers refer to page numbers in the physician package insert, as submitted in Volume 1 of the NDA. We have just received a copy of the currently updated label forwarded by the sponsor to the Division of Reproductive and Urologic Drug Products and we will be discussing additional changes with them internally.

| CHANGE                                                                                                                                                                                                                                                                                                                                                                        | REASON                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Page 13 of 32:</p> <p>Delete [redacted]</p>                                                                                                                                                                                                                                                                                                                                | <p>Reference to the name [redacted] has been removed from the label by HFD-580. An acronym in the label may confuse the clinician. A more specific description of the studied population provides the clinician with a clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p>Page 13 of 32:</p> <p>Insert "A total of [redacted] postmenopausal women with intact uteri and normal baseline bone mineral density ( [redacted] mg/cc) were randomized to FemHRT [redacted] (mg norethindrone acetate/mcg ethinyl estradiol) doses [redacted] placebo, and [redacted] of the randomized population contributed data to the Intent-To-Treat analysis."</p> | <p>A more specific description of the studied population provides the clinician with a clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug.</p> <p><i>Comments to sponsor:</i></p> <ol style="list-style-type: none"> <li>(1) Please supply the correct baseline BMD for this randomized population [redacted] (mg norethindrone acetate/mcg ethinyl estradiol) doses and placebo).</li> <li>(2) The Division of Reproductive and Urologic Drugs (HFD-580) has mentioned that the sponsor may wish to omit the [redacted] from the label. If that is the case, it should be omitted also from this section.</li> <li>(3) Please print in bold "mg" and "mcg" to minimize confusion about the dosages of norethindrone acetate/ ethinyl estradiol</li> </ol> |
| <p>Page 13 of 32:</p> <p>Insert<br/>"(mg norethindrone acetate/mcg ethinyl</p>                                                                                                                                                                                                                                                                                                | <p>The inclusion of this description minimizes confusion about the relative contributions of the progestogen and estrogen in this combination.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

|                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| estradiol)" after FemHRT [redacted]                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p>Page 14 of 32:</p> <p>Delete [redacted]</p>                                                                                                                                                                                                   | <p>(1) The original protocol was designed to compare the BMD of each treatment group to placebo. The original protocol was not designed to account for multiple comparisons of different treatment groups.</p> <p>(2) The [redacted] are not mentioned in this section.</p> <p>(3) Including this reference is confusing to the clinician, particularly since ethinyl estradiol does not have an [redacted] indication.</p>                                                                              |
| <p>Page 14 of 32:</p> <p><i>Please note the following inserted comment:</i></p> <p>[Note to sponsor: Please change ordinate label to "Percent Change in Lumbar Spine Bone Mineral Density from Baseline (+SE) and change table accordingly.]</p> | <p>(1) Quantitative computerized tomography is often used in research studies, but less commonly used in clinical practice. Clinicians may not be familiar with the units.</p> <p>(2) Other labels for drugs with the osteoporosis indication depict "percent change." We understand that the sponsor's primary efficacy for BMD was change in BMD and not percent change in BMD. However, we are trying to maintain consistency across labels to simplify the message for the practicing clinician.</p> |
| <p>Page 14 of 32:</p> <p><i>Please note the following modified figure legend:</i></p> <p>FIGURE 4. [redacted]</p>                                                                                                                                | <p>Title of figure should reflect the presented data.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>Page 14 of 32:</p> <p><i>Please note the following inserted comment:</i></p> <p>[Note to Sponsor: [redacted]]</p>                                                                                                                             | <p>For consistency in the osteoporosis label, the FDA statisticians have recommended the depiction of the Intent To Treat analysis in the label, as this analysis is preferred by the FDA. Please see "E9 Statistical Principles for Clinical Trials", Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98</p>                                                                                                                                                                                         |
| <p><u>General change:</u></p> <p>Order of active ingredient presentation as NA/EE.</p>                                                                                                                                                           | <p>The Division of Metabolic and Endocrine Drug Products understands that the sponsor has discussed this issue with the Division of Reproductive and Urologic Drug Products.</p>                                                                                                                                                                                                                                                                                                                         |

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                           | <p>However, we must comment, as we too feel that placing the progestogen before the estrogen has a precedent in a drug marketed for oral contraception but not in a drug marketed for osteoporosis. The change in the order of the estrogen and progestogen, particularly since there is a 1000 fold difference between the estrogen and progesterone dosage strengths though the actual numbers are of the same order of magnitude, could be misleading to the clinician.</p>                                                                            |
| <p><u>General change:</u></p> <p>Change of Proposed Trade Name FemHRT</p> | <p>The Division of Metabolic and Endocrine Drug Products finds this trade name potentially misleading to the clinician because of the possible implication of "heart" from "HRT".</p> <ol style="list-style-type: none"> <li>(1) Current data regarding the cardiac protective effects of estrogen are still controversial.</li> <li>(2) This NDA was not designed with lipids as a primary efficacy outcome. In general, it is still controversial whether the improvement seen in the lipid profile with estrogen therapy confers a benefit.</li> </ol> |

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2 Page(s) Redacted

Draft

Labeling

Printed by Enid Galliers  
**Electronic Mail Message**

Date: 29-Sep-1999 04:37pm  
From: Marianne Mann  
MANNM  
Dept: HFD-580 PKLN 17B45  
Tel No: 301-827-4260 FAX 301-827-4267

Subject: Re: FWD: Osteoporosis Label Changes

Hi Joanna,  
I read over your comments. Thanks for sharing them. In particular, I agree with your comment regarding page 14 of 32 where you ask the sponsor to delete the sentence: [REDACTED]

I think the sponsor is clearly pushing for the suggestion that Norethindrone acetate [REDACTED] The study was not powered to demonstrate this, however. To me, it's an interesting but exploratory finding. If they wish to confirm this in an additional trial they could, but I don't think they can put it in the label.

My only additional comment is that the Indications and Usage section of the label (page 14) has a lot of "class labeling text" on osteoporosis that is inappropriately placed. Please check some of our other labels (PremPro) to see where this should be placed.

I'm not sure when you intend to share these comments with the sponsor. Please let us know when you do, however.

S Monday-

-MM

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Printed by Enid Galliers  
**Electronic Mail Message** FDA INTERNAL

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Sep-1999 02:43pm  
From: Dornette Spell-LeSane  
SPELLESANED  
Dept: HFD-580 PKLN 17B45  
Tel No: 301-827-4260 FAX 301-827-4267

TO: Enid Galliers ( GALLIERS )  
TO: Joanna Zawadzki ( ZAWADZKIJ )  
CC: Terri Rumble ( RUMBLET )  
Subject: FemHRT update from DRUDP re: name

Hi Enid and Joan,  
Just wanted to let you know that we have just gotten off the phone with  
Parke-Davis informing them of the decision not to accept the name FemHRT  
for the following reasons:

1. LNC found two look-a-likes FemStat and [REDACTED]
2. DDMAC did not like "HRT" because it is a therapeutic indication in  
the name, and,
3. The HRT could be misrepresented as an indication for the heart as HRT  
is used by many as an abbreviation for the heart.

Feel free to contact me for further information  
Dornette Spell-LeSane, PM, DRUDP

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TELECON

NDA 21-102 FemHRT (NETA/EE) tabs

29 Sept. 1999

Between Ross Lobell, P-D (734-622-2111)

AND Joanna Zawadzki, MD, DMEDP  
Enid Galliers, CPMS

We called to request the following additional information regarding the osteoporosis study:

1. Corrected data in Q 3 - Did they have a population for women age 30 and women of comparable age by the same methodology for bone density?. Need reference values. How does the study population compare with the general population, age 30, using the same methodology?
2. In the study report, P. 48, Study 359 do you have the percent responding to tx at 12 and 24 months, the same responder data for the ITT analysis?
3. When you provide characteristics for treatment and placebo groups, do you have the values for the whole group baseline characteristics, LS BMD, for everyone who was randomized? Looking for the average value across the population at baseline.

P-D will respond as soon as the information is available. It may take a day or two.

/S/

Enid Galliers

Cc: Orig. NDA 21-102  
HFD-510/div. File  
HFD-510/EGalliers/JZawadzki

APPEARS THIS WAY  
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 **PARKE-DAVIS**

September 28, 1999

NDA 21-102  
Ref. No. 001  
FemHRT



Re: Withdrawal of FemHRT [redacted]

BL

Solomon Sobel, M.D.  
Director  
Division of Metabolism and Endocrine  
Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Attention: Document Control Room 14B-04  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. Sobel:

We refer to our files for FemHRT and to NDAs 21-102 and 21-065.

Due to the current uncertainty with regard to the recent issue of patent [redacted] and its possible impact on the [redacted] the [redacted] FemHRT, we have decided to discontinue pursuing its registration at this time.

Therefore, we request that the FemHRT [redacted] be withdrawn from both NDA 21-065 and 21-102 without prejudice. We wish to continue ongoing registration activities for the FemHRT 1/5 and [redacted] tablet strengths and look forward to the completion of the Agency's review of these two dose strengths.

Withdrawal of the [redacted] from both NDA 21-065 and 21-102 precludes the need to update our NDA patent disclosure for this product.

Should this dose strength become viable again at a later date, we will submit an sNDA for FDA's review.

Please call either Mr. Ross Lobell 734/622-2111 or Ms. Mary Taylor 734/622-5000 or send a facsimile to 734/622-3283 should you have any questions regarding this submission.

Sincerely,

Ross Lobell  
Senior Manager  
Worldwide Regulatory Affairs

RL:kb 09-28-1999/RN-001/21-102/CI-0376/Letter

**ITEM 13.2.**

**Request and Justification for 3-Year Marketing Exclusivity**

Warner-Lambert Company requests 3 years of market exclusivity for FemHRT™ (hormone replacement therapy, hereafter referred to as HRT). Warner-Lambert Company certifies that the active ingredients in FemHRT™, norethindrone acetate and ethinyl estradiol, meet the criteria for the exclusivity period specified in 21 USC §355(j)(4)(D)(iii) and 355(c)(3)(D)(iii), specifically:

1. No drug product containing the same strengths of active ingredients, norethindrone acetate and ethinyl estradiol, in combination, have been previously approved for which approval is sought in this application. The combination of active ingredients, norethindrone acetate and ethinyl estradiol, have been previously approved.
- 2.a. Four new clinical investigations, other than bioavailability and bioequivalence studies, were submitted to support this application. Warner-Lambert Company certifies that to the best of applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.
- b. The new clinical investigations can be found in Item 8 of the application, NDA No. 21-065, filed concurrently herewith.
- 3.a. Item 8 of the application, NDA 21-065, filed concurrently herewith, list all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to support this application.
- b. Warner-Lambert Company certifies that applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports is complete and accurate.
- c. Warner-Lambert Company certifies that, in applicant's opinion, the present application could not have been approved without the new clinical investigations. The published studies noted in 3.a above are not sufficient to support the approval of the application.

4. Warner-Lambert Company is the sponsor named in Form FDA 1571 for IND  under which the clinical investigation identified in 2 above was performed.

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**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 29-Sep-1999 04:38pm  
**From:** Marianne Mann  
MANNM  
**Dept:** HFD-580 PKLN 17B45  
**Tel No:** 301-827-4260 FAX 301-827-4267

**TO:** Dornette Spell-LeSane ( SPELLLESANED )  
**TO:** Enid Galliers ( GALLIERS.)

**Subject:** FWD: Re: FWD: Osteoporosis Label Changes

Hi Dornette and Enid,  
Attached is my email in response to Joanna. I forgot to cc you both,  
and apologize.

Thanks-MM

APPEARS THIS WAY  
ON ORIGINAL

Printed by Enid Galliers  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 29-Sep-1999 04:16pm  
**From:** Joanna Zawadzki  
ZAWADZKIJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6430 FAX 301-443-9282

**TO:** Marianne Mann ( MANNM )  
**TO:** Dornette Spell-LeSane ( SPELLLESANED )  
**TO:** Daniel Davis ( DAVISD )  
  
**CC:** Enid Galliers ( GALLIERS )  
**CC:** Solomon Sobel ( SOBEL )  
**CC:** Gloria Troendle ( TROENDLE )  
**Subject:** FWD: Osteoporosis Label Changes

The comments and revised label section are now attached.

Thanks.

Joanna

**APPEARS THIS WAY  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: APRIL 30, 2000  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

|                                                                                                                                                                                                                  |                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| NAME OF APPLICANT<br>Parke-Davis Pharmaceutical Research<br>Division of Warner-Lambert Company                                                                                                                   | DATE OF SUBMISSION<br>September 28, 1999                                                                              |
| TELEPHONE NO. (Include Area Code)<br>734/622-2111                                                                                                                                                                | FACSIMILE (FAX) Number (Include Area Code)<br>734/622-3283                                                            |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code<br>or Mail Code, and U.S. License number if previously issued):<br><br>2800 Plymouth Road<br><br>P.O. Box 1047<br><br>Ann Arbor, MI 48106-1047 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City,<br>State, ZIP Code, telephone & FAX number) IF APPLICABLE |

PRODUCT DESCRIPTION

|                                                                                                                                                                        |                                                |                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|----------------------------------|
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-102                                                       |                                                |                                  |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name)<br>norethindrone acetate and ethinyl estradiol                                                                     | PROPRIETARY NAME (trade name) IF ANY<br>FemHRT |                                  |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)<br>(17alpha)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol and<br>(17alpha)-17-(acetyloxy)-19-norpregn-4-en-20-yn-one | CODE NAME (If any)<br>CI-376                   |                                  |
| DOSAGE FORM:<br>Tablets                                                                                                                                                | STRENGTHS:<br>1mg/5µg                          | ROUTE OF ADMINISTRATION:<br>Oral |

PROPOSED INDICATION(S) FOR USE:

Hormone Replacement Therapy

APPLICATION INFORMATION

|                                                                                                       |                                                                                                                                                                                                   |                                                                              |
|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| APPLICATION TYPE (check one)                                                                          | <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)                                                                                                                                     | <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) |
|                                                                                                       | <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)                                                                                                                          |                                                                              |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE                                                              | <input type="checkbox"/> 505 (b) (1)                                                                                                                                                              | <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507            |
| IF AN ANDA, OR AADA, IDENTIFY THE REFERENCES LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION | Name of Drug<br>Holder of Approved Application                                                                                                                                                    |                                                                              |
| TYPE OF SUBMISSION (check one)                                                                        | <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION                                                   |                                                                              |
|                                                                                                       | <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT             |                                                                              |
|                                                                                                       | <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER |                                                                              |

REASON FOR SUBMISSION

Withdrawal

|                                       |                                                                                                                                      |                                                         |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| PROPOSED MARKETING STATUS (check one) | <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx)                                                                                   | <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) |
| NUMBER OF VOLUMES SUBMITTED 1         | THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC |                                                         |

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND's  
NDA's 13-554, 16-776, 16-852, 16-854, 17-354, 17-355, 17-875, 17-876, and 20-130  
DMF's

FORM FDA 356h (7/97)

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j172r011.mdf

This application contains the following items: (Check all that apply)

- ☐ 1. Index
- ☐ 2. Labeling (Check one) ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50 (c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
- ☐ 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
- ☐ 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
- ☐ 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g. CFR 314.50 (f) (1), 21 CFR 601.2)
- ☐ 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306 (k) (1))
- ☐ 17. Field copy certification (21 CFR 314.50 (k) (3))
- ☐ 18. User Fee Cover Sheet (Form 3397)
- ☐ 19. OTHER (Specify) Withdrawal of FemHRT 0.5/2.5 Tablets

#### CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211k, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decisions.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE

Ross Lobell  
Senior Manager  
Worldwide Regulatory Affairs

September 28, 1999

ADDRESS (Street, City, State, and ZIP Code)

2800 Plymouth Road, P.O. Box 1047, Ann Arbor, MI 48106-1047

Telephone Number

( 734 ) 622-2111

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DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0338)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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FORM FDA 356h (7/97)

j172r011.mdf

PAGE 2

# facsimile

TRANSMITTAL

to: Ross Lobell, P-D  
fax #: 734-622-3283  
re: Request for osteoporosis information for NDA 21-102  
date: 24 September 1999  
pages: 8 (including cover page)

Please call if you have any questions.

Thank you.

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Division of Metabolic and Endocrine Drug Products

From the desk of...  
Enid Galliers  
Chief, Project Management Staff (HFD-510)  
DMEDP, ODE II, CDER, FDA  
5600 Fishers Lane, Rm 14B-19  
Rockville, MD 20857

301-827-6429  
Fax 301-443-9282

cc: Orig NDA 21-102  
HFD-510/div. file  
HFD-510/EGalliers

9/24/99

Please provide the following clarifications regarding NDA 21-102 (FemHRT), referring to Study 376-359:

1) Is quantitative computerized tomography method in Study 376-359 single energy or dual energy?

2) Patient Disposition – Table 10, Study 376-359

Please clarify definition of completed study, as n for completed study differs from n for completion of 24 months.

3) Intent-To-Treat Analysis– please clarify corrected data vs uncorrected form 5  
What is Form 5 data?

4) Please indicate where in NDA the following data can be found:

Table of Baseline Patient Characteristics (similar in design to Table 13 – Patient Characteristics for Evaluable Patients) for all randomized patients, with p-values for across groups comparisons

Table of Patient Characteristics (similar in design to Table 13 – Patient Characteristics for Evaluable Patients) for all randomized patients who contribute to Intent-To-Treat analysis, with p-values for across groups comparisons

5) Tables comparable to Table Appendix C-4, Table 17, Table Appendix C-5, Table 14 for Intent-To-Treat, Observed Cases, and Evaluable Analyses with p-values for percent change from baseline:

p-Value (NA/EE or EE vs Placebo)

p-Value (Follow-up vs Baseline)

95% Confidence Interval (NA/EE or EE vs Placebo)

p-Value (NA/EE vs EE)

See attached copies of tables with annotation.

6) Please provide mean baseline lumbar spine bone mineral density  $\pm$  SD for all randomized patients and also for all randomized patients who contributed to Intent-To-Treat Analysis.

7) Please provide mean  $\pm$  SD T-scores (comparison to younger (30 year old), sex-matched controls) and Z-scores (comparison to age-matched and sex-matched controls) for bone mineral density for all randomized patients and also for all randomized patients who contributed to Intent-To-Treat Analysis, if available.

Please provide above data in WORD on disc, also fax hard copies, or send via secure e-mail.  
Thank you.

/S/

9/24/99

For  
Question 2

TABLE 10. Patient Disposition  
[Number (%) of Patients]

|                                            | [Number (%) or Patients] |                              |          |          |          |                        |          |          |          |           |
|--------------------------------------------|--------------------------|------------------------------|----------|----------|----------|------------------------|----------|----------|----------|-----------|
|                                            | Placebo                  | NA/EE Treatment Group, mg/μg |          |          |          | EE Treatment Group, μg |          |          |          | Overall   |
|                                            |                          | 0.2/1                        | 0.5/2.5  | 1/5      | 1/10     | 1                      | 2.5      | 5        | 10       |           |
| Randomized to Treatment                    | 137                      | 139                          | 136      | 146      | 145      | 141                    | 137      | 141      | 143      | 1265      |
| Withdrawals                                |                          |                              |          |          |          |                        |          |          |          |           |
| Adverse Events                             | 14 (10)                  | 14 (10)                      | 11 (8)   | 25 (17)  | 24 (17)  | 18 (13)                | 16 (12)  | 19 (13)  | 30 (21)  | 171 (14)  |
| Sponsor Request <sup>a</sup>               | 0 (0)                    | 0 (0)                        | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)                  | 0 (0)    | 0 (0)    | 96 (67)  | 96 (8)    |
| Personal Reasons                           | 6 (4)                    | 12 (9)                       | 11 (8)   | 7 (5)    | 10 (7)   | 10 (7)                 | 13 (9)   | 7 (5)    | 5 (3)    | 81 (6)    |
| Lost to Follow-up                          | 4 (3)                    | 6 (4)                        | 6 (4)    | 6 (4)    | 5 (3)    | 6 (4)                  | 5 (4)    | 3 (2)    | 4 (3)    | 45 (4)    |
| Lack of Compliance                         | 2 (1)                    | 3 (2)                        | 4 (3)    | 2 (1)    | 3 (2)    | 6 (4)                  | 5 (4)    | 8 (6)    | 2 (1)    | 35 (3)    |
| Lack of Efficacy                           | 3 (2)                    | 0 (0)                        | 1 (1)    | 0 (0)    | 0 (0)    | 2 (1)                  | 1 (1)    | 0 (0)    | 0 (0)    | 7 (1)     |
| Death                                      | 1 (1)                    | 2 (2)                        | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)                  | 0 (0)    | 0 (0)    | 0 (0)    | 3 (0)     |
| Administrative Reasons                     | 0 (0)                    | 1 (1)                        | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)                  | 0 (0)    | 0 (0)    | 1 (1)    | 2 (0)     |
| Unable to Biopsy                           | 0 (0)                    | 0 (0)                        | 0 (0)    | 1 (1)    | 0 (0)    | 0 (0)                  | 0 (0)    | 0 (0)    | 1 (1)    | 2 (0)     |
| Total Withdrawn                            | 30 (22)                  | 38 (27)                      | 33 (24)  | 41 (28)  | 42 (29)  | 42 (30)                | 41 (30)  | 37 (26)  | 139 (97) | 443 (35)  |
| Months of Treatment Completed <sup>b</sup> |                          |                              |          |          |          |                        |          |          |          |           |
| Month 6                                    | 127 (93)                 | 127 (91)                     | 120 (88) | 128 (88) | 116 (80) | 124 (88)               | 122 (89) | 129 (91) | 98 (69)  | 1091 (86) |
| Month 12                                   | 119 (87)                 | 114 (82)                     | 110 (81) | 117 (80) | 111 (77) | 109 (77)               | 112 (82) | 115 (82) | 47 (33)  | 954 (75)  |
| Month 18                                   | 110 (80)                 | 109 (78)                     | 105 (77) | 113 (77) | 107 (74) | 101 (72)               | 101 (74) | 111 (79) | 14 (10)  | 871 (69)  |
| Month 24                                   | 93 (68)                  | 86 (62)                      | 92 (68)  | 93 (64)  | 93 (64)  | 86 (61)                | 84 (61)  | 92 (65)  | 3 (2)    | 722 (57)  |
| Completed Study                            | 108 (79)                 | 102 (73)                     | 103 (76) | 105 (72) | 103 (71) | 99 (70)                | 96 (70)  | 104 (74) | 4 (3)    | 824 (65)  |

<sup>a</sup> The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

<sup>b</sup> Patient's last day on drug ≥ number of months x 30 days/month

<sup>a</sup> The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

<sup>b</sup> Patient's last day on drug ≥ number of months x 30 days/month

FOR QUESTIO. 4

ALL RANDOMIZED - WHO  
ALL RANDOMIZED - WHO  
17

720-03121

p-values

TABLE 13. Summary of Patient Characteristics for Patients With Evaluable Bone-Mineral Density Data Month 24

|                                                     | Placebo     |             | NA/EE Treatment Group, mg/yr |             |             |    | 1/10 |             | 1           |              | 2.5          |             | 5            |    | 10 |    | 695 |  |
|-----------------------------------------------------|-------------|-------------|------------------------------|-------------|-------------|----|------|-------------|-------------|--------------|--------------|-------------|--------------|----|----|----|-----|--|
|                                                     | 86          | 86          | 0.2/1                        | 0.5/2.5     | 1/5         | 89 | 88   | 81          | 81          | 80           | 90           | 90          | 10           | 10 | 10 | 10 | 695 |  |
| Number of Patients With Evaluable Data <sup>a</sup> |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Age, yr                                             |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 51.9 (3.8)  | 52.4 (3.9)  | 51.7 (4.2)                   | 52.0 (3.6)  | 52.1 (3.9)  |    |      | 52.2 (4.1)  | 51.9 (4.2)  | 51.9 (4.2)   | 51.9 (3.8)   | 49.6 (4.8)  | 52.0 (3.9)   |    |    |    |     |  |
| Median (min,max)                                    | 52 (43,61)  | 52 (40,64)  | 53 (40,60)                   | 53 (42,59)  | 52 (42,62)  |    |      | 53 (42,62)  | 52 (40,61)  | 52 (40,61)   | 52 (40,61)   | 51 (40,57)  | 52 (40,64)   |    |    |    |     |  |
| Months Since Last Menstrual Period                  |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 31.2 (17.2) | 33.5 (16.0) | 33.7 (16.0)                  | 29.3 (16.9) | 30.3 (18.4) |    |      | 32.8 (16.3) | 30.3 (17.5) | 32.5 (19.2)  | 32.5 (19.2)  | 24.4 (14.3) | 31.6 (17.2)  |    |    |    |     |  |
| Median (min,max)                                    | 30.0 (2,66) | 33.0 (4,61) | 33.0 (7,62)                  | 28.0 (5,58) | 24.5 (4,65) |    |      | 33.0 (5,60) | 26.5 (3,70) | 32.0 (1,108) | 32.0 (1,108) | 22.5 (6,53) | 30.0 (1,108) |    |    |    |     |  |
| Race, n (%)                                         |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| White                                               | 83 (97)     | 81 (94)     | 78 (92)                      | 85 (96)     | 86 (98)     |    |      | 78 (96)     | 76 (95)     | 86 (96)      | 86 (96)      | 10 (100)    | 663 (95)     |    |    |    |     |  |
| Black                                               | 1 (1)       | 0 (0)       | 3 (4)                        | 2 (2)       | 0 (0)       |    |      | 1 (1)       | 1 (1)       | 2 (2)        | 2 (2)        | 0 (0)       | 10 (1)       |    |    |    |     |  |
| Other                                               | 2 (2)       | 5 (6)       | 4 (5)                        | 2 (2)       | 2 (2)       |    |      | 2 (3)       | 3 (4)       | 2 (2)        | 2 (2)        | 0 (0)       | 22 (3)       |    |    |    |     |  |
| Physically Active, n (%)                            |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Yes                                                 | 57 (66)     | 60 (70)     | 55 (65)                      | 64 (72)     | 53 (60)     |    |      | 53 (65)     | 46 (58)     | 51 (57)      | 51 (57)      | 7 (70)      | 446 (64)     |    |    |    |     |  |
| No                                                  | 29 (34)     | 26 (30)     | 30 (35)                      | 25 (28)     | 35 (40)     |    |      | 28 (35)     | 34 (42)     | 39 (43)      | 39 (43)      | 3 (30)      | 249 (36)     |    |    |    |     |  |
| Smoking History <sup>b</sup> , n (%)                |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Never                                               | 38 (44)     | 47 (55)     | 36 (42)                      | 50 (56)     | 35 (40)     |    |      | 41 (51)     | 34 (42)     | 44 (49)      | 44 (49)      | 3 (30)      | 328 (47)     |    |    |    |     |  |
| Stopped                                             | 24 (28)     | 19 (22)     | 28 (33)                      | 22 (25)     | 26 (30)     |    |      | 28 (35)     | 28 (35)     | 28 (31)      | 28 (31)      | 2 (20)      | 205 (30)     |    |    |    |     |  |
| Light                                               | 5 (6)       | 8 (9)       | 5 (6)                        | 4 (4)       | 3 (3)       |    |      | 3 (4)       | 7 (9)       | 4 (4)        | 4 (4)        | 3 (30)      | 42 (6)       |    |    |    |     |  |
| Moderate                                            | 16 (19)     | 10 (12)     | 10 (12)                      | 10 (11)     | 14 (16)     |    |      | 6 (7)       | 8 (10)      | 9 (10)       | 9 (10)       | 2 (20)      | 85 (12)      |    |    |    |     |  |
| Heavy                                               | 3 (3)       | 2 (2)       | 6 (7)                        | 3 (3)       | 10 (11)     |    |      | 3 (4)       | 3 (4)       | 5 (6)        | 5 (6)        | 0 (0)       | 35 (5)       |    |    |    |     |  |
| Systolic Blood Pressure, mm Hg                      |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 120 (13.5)  | 122 (15.4)  | 120 (17.2)                   | 119 (13.2)  | 121 (14.7)  |    |      | 121 (14.0)  | 119 (13.6)  | 119 (13.6)   | 119 (13.5)   | 112 (9.5)   | 120 (14.4)   |    |    |    |     |  |
| Diastolic Blood Pressure, mm Hg                     |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 75.5 (8.8)  | 76.5 (8.4)  | 75.2 (8.8)                   | 74.8 (8.6)  | 76.5 (8.2)  |    |      | 75.8 (9.1)  | 75.8 (8.4)  | 76.7 (8.6)   | 76.7 (8.6)   | 75.4 (12.0) | 75.8 (8.6)   |    |    |    |     |  |
| Weight, kg                                          |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 64.9 (8.6)  | 65.8 (8.6)  | 65.6 (9.1)                   | 64.7 (8.9)  | 64.8 (9.4)  |    |      | 66.6 (8.9)  | 64.2 (9.1)  | 65.5 (9.6)   | 65.5 (9.6)   | 60.8 (7.5)  | 65.2 (9.0)   |    |    |    |     |  |
| Height, cm                                          |             |             |                              |             |             |    |      |             |             |              |              |             |              |    |    |    |     |  |
| Mean (SD)                                           | 164.2 (7.4) | 165.2 (5.5) | 163.5 (5.9)                  | 163.0 (7.9) | 163.9 (6.6) |    |      | 164.9 (6.1) | 163.4 (5.8) | 164.4 (6.4)  | 164.4 (6.4)  | 160.9 (6.2) | 164.0 (6.5)  |    |    |    |     |  |

SD = Standard deviation.

<sup>a</sup> The 10 µg EE group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

<sup>b</sup> Light = 1 to 10 cigarettes/day; Moderate = 11 to 20 cigarettes/day; Heavy = ≥21 cigarettes/day.

SD = Standard deviation.  
<sup>a</sup> The 10 mg EE group was terminated early (per pmico) due to an unacceptably high rate of endometrial hyperplasia.  
<sup>b</sup> Light = 1 to 10 cigarettes/day; Moderate = 11 to 20 cigarettes/day; Heavy = ≥21 cigarettes/day.

## APPENDIX C.4

**SUMMARY OF MEAN (SE) AND ADJUSTED (LEAST-SQUARES ESTIMATE)  
MEAN (SE) CHANGE IN BONE-MINERAL DENSITY (MG/CC) BASED ON CORRECTED DATA IF AVAILABLE  
INTENT-TO-TREAT POPULATION**

| Time                                              | NA/EE Treatment Group |              |              |              | EE Treatment Group |              |              |              |
|---------------------------------------------------|-----------------------|--------------|--------------|--------------|--------------------|--------------|--------------|--------------|
|                                                   | Placebo               | 0.2/1        | 0.5/2.5      | 1/5          | 1/10               | 1            | 2.5          | 5            |
| <b>Mean Bone-Mineral Density</b>                  |                       |              |              |              |                    |              |              |              |
| Month 24                                          |                       |              |              |              |                    |              |              |              |
| N                                                 | 123                   | 119          | 120          | 124          | 118                | 119          | 120          | 121          |
| Baseline                                          | 119.5 (2.03)          | 120.2 (1.79) | 119.8 (1.85) | 117.8 (1.56) | 119.4 (1.86)       | 119.8 (1.73) | 116.9 (1.63) | 119.1 (1.79) |
| Follow-Up                                         | 111.8 (2.14)          | 116.9 (1.71) | 117.4 (1.80) | 121.0 (1.86) | 124.2 (2.06)       | 116.9 (1.96) | 114.4 (1.87) | 117.2 (2.08) |
| Change From Baseline                              | -7.7 (1.24)           | -3.3 (1.45)  | -2.4 (1.37)  | 3.1 (1.24)   | 4.8 (1.32)         | -2.9 (1.43)  | -2.5 (1.07)  | -1.8 (1.57)  |
| Percent Change                                    | -6.3 (1.10)           | -2.1 (1.03)  | -0.8 (1.49)  | 3.1 (1.11)   | 4.5 (1.13)         | -2.0 (1.27)  | -2.0 (0.92)  | -0.9 (1.56)  |
|                                                   |                       |              |              |              |                    |              |              | 2.5 (0.79)   |
| <b>Adjusted Mean Bone-Mineral Density</b>         |                       |              |              |              |                    |              |              |              |
| Month 24                                          |                       |              |              |              |                    |              |              |              |
| N                                                 | 123                   | 119          | 120          | 124          | 118                | 119          | 120          | 121          |
| Change From Baseline                              | -5.7 (1.16)           | -1.8 (1.19)  | -0.8 (1.18)  | 4.6 (1.16)   | 6.5 (1.18)         | -1.6 (1.19)  | -1.2 (1.18)  | -0.2 (1.18)  |
| p-Value* (NA/EE or EE vs Placebo)                 |                       | 0.0308       | 0.0046       | 0.0001       | 0.0001             | 0.0207       | 0.0098       | 0.0012       |
| p-Value* (Follow-up vs Baseline)                  | 0.0001                | 0.1206       | 0.5079       | 0.0001       | 0.0001             | 0.1817       | 0.3205       | 0.8958       |
| 95% Confidence Interval* (NA/EE or EE vs Placebo) |                       | [0.3, ∞]     | [1.4, ∞]     | [6.8, ∞]     | [8.6, ∞]           | [0.6, ∞]     | [1.0, ∞]     | [2.0, ∞]     |
| p-Value* (NA/EE vs EE)                            |                       | 0.8740       | 0.8123       | 0.0034       | 0.2185             |              |              |              |
|                                                   |                       |              |              |              |                    |              |              | [6.4, ∞]     |

SE = Standard error.

- \* The 10 µg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.
- \* The null hypothesis is that the mean changes in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.
- \* The null hypothesis is that the mean change from baseline is equal to zero.
- \* For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.
- \* The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

p-values for percent change from baseline:

p-Value (NA/EE or EE vs Placebo)

p-Value (Follow-up vs Baseline)

95% Confidence Interval (NA/EE or EE vs Placebo)

p-Value (NA/EE vs EE)

for  
QUESTIONS

TABLE 17. Summary of Mean (SE) Uncorrected Form 5 Bone-Mineral Density  
Intent-to-Treat Population

| Time                        | NA/EE Treatment Group, mg/μg |              |              |              | EE Treatment Group, μg |              |              |              |                 |
|-----------------------------|------------------------------|--------------|--------------|--------------|------------------------|--------------|--------------|--------------|-----------------|
|                             | Placebo                      | 0.2/1        | 0.5/2.5      | 1/5          | 1/10                   | 1            | 2.5          | 5            | 10 <sup>a</sup> |
| Month 24                    |                              |              |              |              |                        |              |              |              |                 |
| N                           | 123                          | 119          | 120          | 124          | 118                    | 119          | 120          | 121          | 100             |
| Baseline, mg/cc             | 124.8 (1.98)                 | 123.4 (1.64) | 125.4 (1.89) | 123.3 (1.57) | 124.9 (1.80)           | 125.0 (1.69) | 121.6 (1.91) | 123.1 (1.79) | 125.7 (1.94)    |
| Follow-Up, mg/cc            | 117.9 (2.22)                 | 121.9 (1.85) | 123.4 (1.80) | 128.0 (1.98) | 131.5 (2.33)           | 121.4 (2.03) | 120.1 (2.08) | 120.9 (2.09) | 129.4 (2.17)    |
| Change From Baseline, mg/cc | -6.9 (1.39)                  | -1.5 (1.23)  | -2.0 (1.37)  | 4.8 (1.29)   | 6.5 (1.51)             | -3.6 (1.40)  | -1.6 (1.21)  | -2.2 (1.54)  | 3.6 (1.05)      |
| Percent Change              | -5.4 (1.09)                  | -0.9 (0.98)  | -0.8 (1.10)  | 4.0 (1.07)   | 5.4 (1.19)             | -2.6 (1.11)  | -1.0 (0.97)  | -1.4 (1.29)  | 3.0 (0.84)      |

of endometrial hyperplasia.

p-values for percent change from baseline:

p-Value (NA/EE or EE vs Placebo)

p-Value (Follow-up vs Baseline)

95% Confidence Interval (NA/EE or EE vs Placebo)

p-Value (NA/EE vs EE)

For  
Question

From Baseline in Uncorrected Form 5 Bone-

lation

| Time                                                                  | Placebo     | NA/EE Treatment Group, mg/μg |             |            |            | EE Treatment Group, μg |             |             |                 |
|-----------------------------------------------------------------------|-------------|------------------------------|-------------|------------|------------|------------------------|-------------|-------------|-----------------|
|                                                                       |             | 0.2/1                        | 0.5/2.5     | 1/5        | 1/10       | 1                      | 2.5         | 5           | 10 <sup>a</sup> |
| Month 24                                                              |             |                              |             |            |            |                        |             |             |                 |
| N                                                                     | 123         | 119                          | 120         | 124        | 118        | 119                    | 120         | 121         | 100             |
| Change From Baseline, mg/cc                                           | -4.8 (1.18) | -0.2 (1.21)                  | -0.5 (1.20) | 6.3 (1.18) | 8.2 (1.20) | -2.3 (1.21)            | -0.6 (1.20) | -0.6 (1.20) | 5.6 (1.31)      |
| p-Value <sup>b</sup> (NA/EE or EE vs Placebo)                         | ..          | 0.0094                       | 0.0162      | 0.0001     | 0.0001     | 0.1786                 | 0.0183      | 0.0175      | 0.0001          |
| 95 % Confidence Interval <sup>c</sup> (NA/EE or EE vs Placebo), mg/cc | ..          | [1.0, ∞]                     | [0.7, ∞]    | [7.6, ∞]   | [9.4, ∞]   | [-1.0, ∞]              | [0.7, ∞]    | [0.7, ∞]    | [6.7, ∞]        |
| p-Value <sup>d</sup> (Follow-up vs Baseline)                          | 0.0001      | 0.8749                       | 0.6656      | 0.0001     | 0.0001     | 0.0604                 | 0.6274      | 0.6416      | 0.0001          |
| p-Value <sup>e</sup> (NA/EE vs EE)                                    | ..          | 0.2087                       | 0.9706      | 0.0001     | 0.1437     | ..                     | ..          | ..          | ..              |

SE = Standard error.

<sup>a</sup> The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

<sup>b</sup> The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.

<sup>c</sup> For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.

<sup>d</sup> The null hypothesis is that the mean change from baseline is equal to zero.

<sup>e</sup> The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

APPENDIX C.5  
SUMMARY OF MEAN (SE) BONE-MINERAL DENSITY (MG/CC)  
OBSERVED CASES DATA

| Time                           | Placebo      | NA/EE Treatment Group |              |              |              | EE Treatment Group |              |              |              |
|--------------------------------|--------------|-----------------------|--------------|--------------|--------------|--------------------|--------------|--------------|--------------|
|                                |              | 0.2/1                 | 0.5/2.5      | 1/5          | 1/10         | 1                  | 2.5          | 5            | 10*          |
| Corrected Bone-Mineral Density |              |                       |              |              |              |                    |              |              |              |
| Month 12                       |              |                       |              |              |              |                    |              |              |              |
| N                              | 109          | 105                   | 110          | 111          | 105          | 108                | 111          | 112          | 60           |
| Baseline                       | 119.6 (2.23) | 119.6 (1.73)          | 119.6 (1.96) | 118.7 (1.61) | 119.8 (2.03) | 118.9 (1.84)       | 117.0 (1.70) | 118.3 (1.85) | 119.2 (2.68) |
| Follow-Up                      | 115.6 (2.38) | 117.7 (1.93)          | 119.4 (1.93) | 123.3 (1.81) | 124.9 (2.11) | 118.0 (2.08)       | 116.1 (1.79) | 117.8 (2.01) | 122.4 (2.87) |
| Change From Baseline           | -3.9 (0.91)  | -1.9 (1.09)           | -0.1 (1.40)  | 4.6 (0.91)   | 5.2 (1.13)   | -0.9 (1.09)        | -0.9 (0.87)  | -0.5 (1.03)  | 3.2 (1.32)   |
| Percent Change                 | -3.5 (0.84)  | -1.5 (0.92)           | 0.9 (1.24)   | 3.9 (0.83)   | 4.8 (1.00)   | -0.8 (0.94)        | -0.6 (0.75)  | -0.2 (0.89)  | 3.0 (1.20)   |
| Month 24                       |              |                       |              |              |              |                    |              |              |              |
| N                              | 97           | 99                    | 99           | 102          | 98           | 96                 | 92           | 105          | 14           |
| Baseline                       | 120.4 (2.47) | 120.2 (2.01)          | 118.3 (2.05) | 118.7 (1.72) | 117.9 (2.06) | 119.3 (1.97)       | 116.3 (1.79) | 118.7 (1.95) | 113.4 (6.02) |
| Follow-Up                      | 112.5 (2.53) | 116.1 (1.92)          | 116.1 (1.94) | 121.2 (2.02) | 122.8 (2.30) | 116.1 (2.19)       | 113.3 (2.14) | 117.3 (2.26) | 116.9 (6.76) |
| Change From Baseline           | -7.9 (1.43)  | -4.1 (1.66)           | -2.2 (1.54)  | 2.5 (1.41)   | 4.9 (1.40)   | -3.2 (1.72)        | -2.9 (1.28)  | -1.3 (1.71)  | 3.5 (3.20)   |
| Percent Change                 | -6.4 (1.27)  | -2.8 (1.15)           | -0.5 (1.74)  | 2.6 (1.27)   | 4.6 (1.24)   | -2.0 (1.54)        | -2.4 (1.09)  | -0.5 (1.73)  | 3.2 (2.82)   |

SE = Standard error.

\* The 10 µg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia.

p-values for percent change from baseline:

p-Value (NA/EE or EE vs Placebo)

p-Value (Follow-up vs Baseline)

95% Confidence Interval (NA/EE or EE vs Placebo)

p-Value (NA/EE vs EE)

for Question 5

TABLE 14. Summary of Mean (SE) Bone-Mineral Density Evaluable Data

| Time                        | NA/EE Treatment Group, mg/μg |              |              |              |              | EE Treatment Group, μg |              |              |              |  |
|-----------------------------|------------------------------|--------------|--------------|--------------|--------------|------------------------|--------------|--------------|--------------|--|
|                             | Placebo                      | 0.2/1        | 0.5/2.5      | 1/5          | 1/10         | 1                      | 2.5          | 5            | 10*          |  |
| Month 12                    |                              |              |              |              |              |                        |              |              |              |  |
| N                           | 98                           | 94           | 93           | 96           | 92           | 92                     | 96           | 99           | 51           |  |
| Baseline, mg/cc             | 120.5 (2.36)                 | 120.1 (1.84) | 119.1 (2.20) | 117.8 (1.78) | 118.8 (2.23) | 117.7 (2.02)           | 117.0 (1.72) | 117.8 (2.01) | 120.1 (2.99) |  |
| Follow-up, mg/cc            | 115.9 (2.54)                 | 117.7 (2.02) | 118.7 (2.14) | 122.1 (1.96) | 123.2 (2.24) | 115.7 (2.22)           | 115.9 (1.85) | 117.0 (2.11) | 123.6 (3.30) |  |
| Change From Baseline, mg/cc | -4.6 (0.94)                  | -2.4 (1.15)  | -0.4 (1.57)  | 4.2 (0.89)   | 4.4 (1.13)   | -2.0 (1.17)            | -1.2 (0.93)  | -0.8 (0.97)  | 3.5 (1.36)   |  |
| Percent Change              | -4.1 (0.85)                  | -1.9 (0.98)  | 0.8 (1.41)   | 3.5 (0.85)   | 4.3 (1.02)   | -1.7 (1.02)            | -0.9 (0.80)  | -0.5 (0.84)  | 3.1 (1.21)   |  |
| Month 24                    |                              |              |              |              |              |                        |              |              |              |  |
| N                           | 86                           | 86           | 85           | 89           | 88           | 81                     | 80           | 90           | 10           |  |
| Baseline, mg/cc             | 121.6 (2.63)                 | 120.0 (1.96) | 117.5 (2.24) | 118.2 (1.87) | 117.2 (2.24) | 118.2 (2.19)           | 116.4 (1.81) | 117.5 (2.12) | 112.9 (8.23) |  |
| Follow-up, mg/cc            | 112.5 (2.71)                 | 115.4 (2.01) | 115.3 (2.03) | 120.2 (2.16) | 121.5 (2.39) | 114.8 (2.35)           | 113.3 (2.31) | 115.1 (2.30) | 115.5 (8.41) |  |
| Change From Baseline, mg/cc | -9.1 (1.54)                  | -4.6 (1.23)  | -2.1 (1.68)  | 2.0 (1.49)   | 4.3 (1.41)   | -3.4 (1.85)            | -3.1 (1.43)  | -2.4 (1.66)  | 2.6 (3.81)   |  |
| Percent Change              | -7.4 (1.37)                  | -3.6 (0.99)  | -0.2 (1.95)  | 2.2 (1.36)   | 4.2 (1.27)   | -2.1 (1.68)            | -2.7 (1.20)  | -1.3 (1.82)  | 2.7 (3.49)   |  |

\* Standard error.

\* The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

p-values for percent change from baseline:

p-Value (NA/EE or EE vs Placebo)

p-Value (Follow-up vs Baseline)

95% Confidence Interval (NA/EE or EE vs Placebo)

p-Value (NA/EE vs EE)

for QUESTION 5

NDA 21-102 FemHRT  
(norethindrone acetate[NA]/ethinyl estradiol[EE] tablets)

September 24, 1999  
Parke-Davis  
4:05 - 4:10 PM

**MEMORANDUM OF TELECON**

**FDA Participants:**

Joanna Zawadzki, MD, Medical Officer, DMEDP  
Enid Galliers, CPMS, DMEDP

**Parke-Davis Participants:**

Mary O'Sullivan  
Mary O'Keefe, Biostatistics  
Ross Lobell, Senior Manager, Worldwide Regulatory Affairs

**Purpose:** To clarify bone mineral density (BMD) data and their presentation in labeling.

**Discussion:** FDA commented that the BMD data had been given in a range, and asked Parke-Davis if they had done T-score or Z-score.

Parke-Davis replied that they didn't know but would find out and let FDA know.

/S/

Enid Galliers, CPMS, DMEDP

CC: Orig. NDA 21-102  
HFD-510/div. Files

**APPEARS THIS WAY  
ON ORIGINAL**



September 22, 1999

C

NDA-21-102  
FemHRT

Re: Electronic Desk Copy

Enid Galliers  
Supervisor, Consumer Safety Officer  
Division of Metabolism and Endocrine  
Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Attention: Document Control Room 14B-04  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Ms. Galliers:

Reference is made to our files for NDA 21-102 for FemHRT.

Per your request, we are providing the Integrated Summary of Safety and the Risk/Benefit Summary in the form of CD-ROM.

Should you have any questions regarding this submission please contact me at 734/622-2514 or Ross Lobell at 734/622-2111.

Sincerely,

Mary O'Sullivan, MPH  
Manager  
Worldwide Regulatory Affairs

MO:kb  
09-22-1999\21-102\CI-0376\Letter

Attachment

# facsimile

TRANSMITTAL

**to:** Russ Lobel, Parke-Davis  
**fax #:** 734-622-3283 (Phone: 734-622-2111)  
**re:** Request for e-files  
**date:** 16 Septmeber 1999  
**pages:** 2 (including cover page)

Would it be possible for you to provide by sometime early next week a diskette with the study report and individual tables and documents from the appendices requested on the attached sheet prepared by Dr. Zawadzki.

It would greatly accelerate the completion of her review if you could do so (especially if the documents are in MS Word 6 or 7).

Thank you



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**Division of Metabolic and Endocrine Drug Products**

*From the desk of...*

*Enid Galliers*

*email- GALLIERS@CDER.FDA.GOV* Chief, Project Management Staff (HFD-510)  
DMEDP, ODE II, CDER, FDA  
5600 Fishers Lane, Rm 14B-19  
Rockville, MD 20857

301-827-6429

Fax: 301-443-9282

9/16/99

Request for Submission of Selected Pages of NDA 21-102 (NDA 21-065) in electronic format, preferably as WORD document:

| <b>Description</b>                             | <b>Pages of NDA<br/>(Volume), Page Number(s)<br/>in Square blocks</b> | <b>(volume)<br/>Page of actual document</b> |
|------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------|
| Protocol 376-359 Study Report                  | (vol. 77) 1-163                                                       |                                             |
| Protocol 376-359 and Amendments 1,2,3,4        |                                                                       | (vol. 77) 173-204                           |
| Guidelines for Quality Assurance Measurements  |                                                                       | (vol. 77) 217-221                           |
| Criteria for Exclusion from Evaluable Analyses |                                                                       | (vol. 78) 381-4                             |
| Appendix B – Patient Narratives                |                                                                       | (vol. 78) 554-656                           |
| Appendix C Summary Tables                      |                                                                       | (vol. 78) 658-664<br>677-682<br>723- 738    |
| Appendix D Statistical Methodology             |                                                                       | (vol. 79) 807-822                           |
| ISS                                            | (vol. 50) 1-118                                                       |                                             |
| Integrated Risk/Benefit Assess                 | (vol 51) 203-218                                                      |                                             |

NDA 21-102

NDA 21-065

JUL 7 1999

Parke-Davis Pharmaceutical Research  
Attention: Mary E. Taylor, M.P.H.  
Director, Worldwide Regulatory Affairs  
2800 Plymouth Road  
P.O. Box 1047  
Ann Arbor, MI 48105-1047

Dear Ms. Taylor:

We have received your new drug application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: FemHRT (norethindrone acetate+ethinyl estradiol) Tablets,  
[redacted] 1 mg+5mcg, [redacted]

Review Priority Classification: Standard (S)

Date of Application: December 16, 1998

Date of Receipt: December 17, 1998

Our Reference Number: NDA 21-102

Because the clinical expertise for reviewing the indication of postmenopausal osteoporosis prevention is not located in the division responsible for your original new drug application, NDA 21-065, the referenced indication will be reviewed by the Division of Metabolic and Endocrine Drug Products. We have unbundled your application for our administrative convenience, and therefore no additional user fee will be charged. Any amendments you make for this indication should be submitted to this new application at the address below.

This application was filed under section 505(b) of the Act on February 15, 1999, in accordance with 21 CFR 314.101(a). The primary user fee goal date is October 17, 1999, and the secondary user fee goal date is December 17, 1999.

NDA 21-102

Page 2

Please cite the new NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, contact Randy Hedin, Regulatory Project Manager, at 301-827-6392.

Sincerely yours,

/S/

7.7.99

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-102  
HFD-510/Div. Files  
HFD-580/Div. Files  
HFD-510/CPMS  
HFD-510/CSO-Hedin  
HFD-510/Reviewers and Team Leaders  
Archival NDA 21-065  
HFD-580/ Div. File  
HFD-580/CPMS/CSO  
DISTRICT OFFICE

Drafted by:emg/7.7.99

**APPEARS THIS WAY  
ON ORIGINAL**

ACKNOWLEDGEMENT (AC)

NDA 21-102 *femhrt*

For additional safety evaluation, refer to the Medical Officer's Review  
of NDA 21-065 *femhrt*.

APPEARS THIS WAY  
ON ORIGINAL

## **NDA 21-102 femhrt**

The safety update for the studies covered by this application was submitted on April 15, 1999, to NDA 21-065 and was reviewed by the medical officer in DRUDP assigned to that NDA. Dr. D. Davis found the safety update satisfactory in his review dated October 14, 1999, of that NDA.

**APPEARS THIS WAY  
ON ORIGINAL**

## **NDA 21-102**

The Division Director's signature on the action letter replaces this memorandum.

**APPEARS THIS WAY  
ON ORIGINAL**

## **NDA 21-102**

The Team Leader's signature on the medical review replaces this memorandum.

**APPEARS THIS WAY  
ON ORIGINAL**

## **NDA 21-102**

This section is not needed or not applicable to this application.

**APPEARS THIS WAY  
ON ORIGINAL**

## **NDA 21-102**

This section is not needed or not applicable to this application.

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-102 *femhrt*

Advertising and promotional materials have not been submitted.

APPEARS THIS WAY  
ON ORIGINAL

"FemHRT" but they would commit to changing all packaging with the FDA's suggestion of "femhrt" as soon as possible or within 6 months. The Divisions did not agree with this proposal because they remained concerned that the product name would be fairly well established in the first 6 months of marketing as "FemHRT". The Divisions requested the firm change the name to "femhrt" immediately for all packaging and promotional materials but clarified that we could accept the inner foil reading "femHRT" until the new foil could be printed.

## II. SAFETY AND RISK ASSESSMENT:

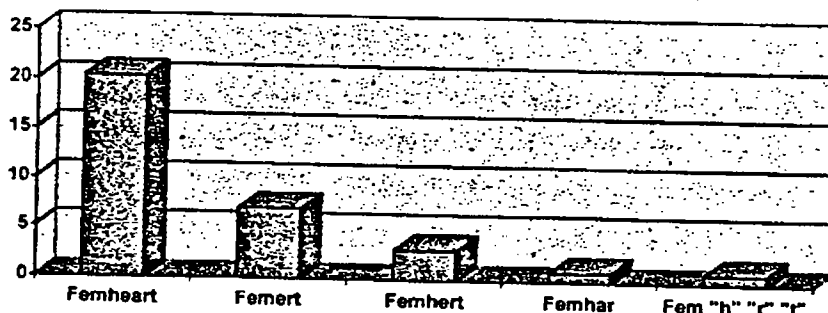
1. An internal study was conducted within OPDRA to evaluate the proposed proprietary name and determine how the proposed name would be pronounced. This analysis was conducted to determine if the new presentation of the name would still have the connotation of "heart" associated with it.

### Methodology:

A study was conducted for the proposed name "femhrt" involving 14 health care practitioners within OPDRA. The participants were comprised of pharmacists, physicians and nurses. Participants were contacted via phone and e-mail. The first group contacted, via telephone, were informed OPDRA had an established name they were evaluating and wanted their interpretation of the name pronunciation. The name was then spelled "femhrt", at that point every participant questioned the spelling of the proposed name. OPDRA stated the spelling was correct and they in turn provided their verbal interpretation of the pronunciation of the proposed name. The second group of participants were e-mailed and informed that OPDRA had a proprietary name "femhrt" that they were evaluating and needed their interpretation of the name pronunciation. Each individual was instructed to telephone OPDRA with their response.

### Results:

Thirteen out of fourteen individuals responded to the survey. 1% responded with the name pronunciation that the Division most likely expected, "femhert". 54% responded with the pronunciation of "femheart". 23% responded with "femert", 1% responded with "Femhar" and 1% responded with [Fem "h" "r" "t"].



### Analysis:

54% of the participants pronounced the drug name "femheart". Most participants stated the spelling of the drug name made no sense to them and did not appear to be grammatically correct and needed to confirm the spelling prior to providing their responses. The responses did not contain any names that had the potential to be confused with any approved or pending drug products. The decrease in the prominence of "hrt" appears to not have made a significant difference in the pronunciation of the name. Most health care practitioners will probably pronounce "femhrt" as "femheart". These

findings substantiate the Division's original concerns when the name was originally proposed as "FemHRT".

2. A search of the American Drug Index (43rd Edition), Physicians' Desk Reference [53 Edition; 1999] and Drug Facts and Comparisons (Updated Monthly) for potential sound-alike or look-alike names to approved drugs was completed. The findings were discussed in a focal group within OPDRA.

In OPDRA's opinion, [ ] and Femstat, could possibly pose a problem with confusion when written. OPDRA believes a written analysis would be needed to assess the degree to which these proprietary names might be confused. (i.e., overlapping strengths, etc.). Written analysis studies require more review time and due to time constraints with this review, a written analysis was not performed.

3. A search of the Agency's internal databases, Establishment Evaluation System (EES), Drug Product Reference File (DPR), and the Labeling and Nomenclature Committee database (LNC) for potential sound-alike or look-alike names to unapproved/approved drugs did not reveal any potential problems with sound-alike/look-alike issues.

### III. RECOMMENDATIONS:

1. From a safety perspective, OPDRA believes the use of the proposed proprietary name "femhrt" poses no significant safety risk.
2. After review of the results of the study, OPDRA concludes "femhrt" will most likely be pronounced as "femheart". From a promotional perspective, OPDRA believes this is unacceptable. The firm may possibly promote cardiac claims given "heart" is associated with the pronunciation of the name. In addition, the name may also be considered misleading in that it implies some effect on the "heart".
3. We recognize the Division's decision to accept the name "femhrt". If this name is utilized, OPDRA recommends the firm be requested to introduce the phonetic spelling of the pronunciation of "femhrt" on promotional, carton and insert labeling (i.e. fem ert). This might diminish the likelihood of mispronunciation of the name as "femheart" and hopefully help eliminate the concerns surrounding the cardiac promotional claims.

**APPEARS THIS WAY  
ON ORIGINAL**

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

/S/

Carol Holquist, RPh  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

10/12/99

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files  
HFD-510; Lanh Green, Safety Evaluator, DDRE II, OPDRA  
HFD-580; Denise Toyer, Safety Evaluator, DDRE II, OPDRA  
HFD-400; Jerry Phillips, Associate Director, OPDRA  
HFD-400; Peter Honig, Deputy Director, OPDRA  
HFD-002; Murray Lumpkin, Acting Director, OPDRA

APPEARS THIS WAY  
ON ORIGINAL

**PARKE-DAVIS**

December 16, 1998

NDA 21-065

Ref. No. 001

FemHRT™ (norethindrone acetate and  
ethinyl estradiol tablets, USP)

Re: Original New Drug Application  
User Fee I.D. No. 3617

Food and Drug Administration  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20852

*Rec'd*  
DEC 18 1998  
*HFD-510*

*Rec'd*  
DEC 17 1998  
*CDE*

Dear Sir/Madam:

Pursuant to 505(b)(1) of the FDC Act, enclosed is a new drug application (21-065) for FemHRT™ (norethindrone acetate and ethinyl estradiol tablets, USP). This NDA provides evidence for the use of FemHRT in women with intact uteri for the treatment of moderate to severe vasomotor symptoms associated with menopause [redacted] and prevention of osteoporosis.

The NDA number 21-065 was preassigned to this application on October 28, 1998.

FemHRT has been investigated by Parke-Davis under IND [redacted]. Please also refer to our approved NDA 17-876 for Loestrin® and our withdrawn NDA 13-554 Norlestrin® for information on Nonclinical Pharmacology and Toxicology (NDA Item 5) for the active drug substances in FemHRT (norethindrone acetate and ethinyl estradiol).

As required under the Prescription Drug User Fee Act II, a check for [redacted] (check number [redacted]) has been sent to the Food and Drug Administration in care of Mellon Bank, Philadelphia, Pennsylvania on December 8, 1998. The User ID number is 3617.

Parke-Davis has met with the Division of Metabolic and Endocrine Drug Products and the Division of Reproductive and Urologic Drug Products on numerous occasions during the development of FemHRT. These meetings, described in detail in Item 3, included an End-of-Phase 2 meeting in July 1988, 2 meetings to further refine study design and discuss handling of cases of endometrial hyperplasia in Study 376-359, 2 meetings to discuss the content, format, and fileability of the NDA, and a pre-NDA meeting in September 1992. At the pre-NDA meeting, Parke-Davis was informed that severity of hot flash frequency was a required endpoint for the vasomotor indication. Since the previous

pivotal hot flash study (376-368) had evaluated only the frequency of hot flashes, a new study (376-390) including severity was initiated in January 1996. At a second pre-NDA meeting in June 1996 plans for the content and format of the NDA were discussed and an October 1996 submission date was proposed.

In July 1996, the [ ] facility that had been the manufacturing site for FemHRT was closed. The manufacturing site for FemHRT was then moved to Duramed in Cincinnati, Ohio. At a January 15, 1998 meeting with the FDA, it was agreed that FDA would accept data from batches manufactured at [ ] to support the [ ] month shelf life. Parke-Davis also agreed to submit data for 9 batches, 3 of each strength, manufactured at Duramed. The FDA also requested that one batch of each strength must have 3-months room temperature and accelerated data at time of NDA submission which was targeted for December 1998.

Ms. Diane Moore of the Division of Reproductive and Urologic Drug Products (DRUDP) notified Ms. Robin Pitts of Parke-Davis on January 9, 1997 that the trade name FemHRT™ was deemed acceptable by the nomenclature committee and DRUDP.

Reference is also made to our letter of July 30, 1998 (IND [ ] Attachment A). This letter outlined agreements made at the pre-NDA meeting on June 3, 1996 regarding what electronic data files would be provided at the time of the NDA submission. On August 11, 1998, Ms. Diane Moore of DRUDP contacted Ms. Robin Pitts of Parke-Davis and informed her the electronic files listed in the July 30, 1998 submission were adequate. On December 1, 1998 Dr. Ortwerth of DRUDP requested an additional review aid for Item 4 CMC section. In a follow up conversation on December 10, 1998 between Ms. Diane Moore and Ms. Robin Pitts, it was agreed that this additional review aid would be submitted by December 28, 1998.

In accordance with the September 1997 "Guidance to Industry-Archiving Submissions in Electronic Format-NDAs," we have submitted an electronic archive that contains the following:

- Case Report Forms (CRFs) for all patients who died during a clinical study or who withdrew from a study due to an adverse event.
- Data Listings or Case Report Tabulations (CR Tabs)

A description of the electronic archive of the FemHRT Electronic Regulatory Submission (ERS) is found in Attachment B.

Food and Drug Administration  
NDA 21-065  
December 16, 1998  
Page 3

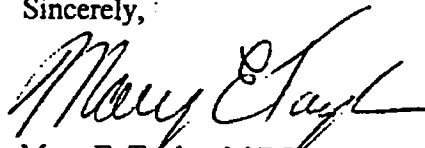
In addition to the User Fee Cover Sheet (Item 18), Patent and Exclusivity information (Item 13), Debarment Certification (Item 16), and the Field Copy Certification (Item 17) are located in Volume 1. Please refer to the attached Form FDA 356h and the NDA Index which detail the complete contents of this NDA. At the request of Ms. Diane Moore, Project Manager, 5 copies of Volumes 1 and 2 are provided as desk copies.

Pursuant to 21 CFR 314.440, a complete copy of the Chemistry, Manufacturing and Controls section of this NDA has been sent to the FDA District Offices in Newark, New Jersey, and Cincinnati, Ohio.

Copies of all DMF letters referenced in this NDA are located in Item 4 as well as provided immediately following this cover letter (Attachment C).

For any questions regarding this submission during the NDA review, please contact either myself at 734/622-5000, or via FAX at 734/622-3283, or Ms. Robin Pitts at 734/622-5628.

Sincerely,



Mary E. Taylor, M.P.H.  
Director  
Worldwide Regulatory Affairs

MET/dp  
c:\nda\21-065\121698-001  
Attachments

**NDA Copies**

Desk Copies (5) Volumes 1 and 2  
"Blue" Archive Vol. 1-153  
"Red" Chemistry Vol. 1 and 3-21  
"Orange" Biopharmaceutics Vol. 1 and 22-48  
"Tan" Medical Vol. 1 and 49-109  
"Green" Biometrics Vol. 1 and 110-53  
"Maroon" Field (Newark) 1-21  
"Maroon" Field (Cincinnati) 1-21

**APPEARS THIS WAY  
ON ORIGINAL**



OFFICES OF DRUG EVALUATION  
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT  
ACTION PACKAGE CHECKLIST

NDA 21-102 Drug: ferm-hrt <sup>1mg</sup> norethandione acetate  
Parker Davis Chem/Ther/other Types: 6 S  
CSO/PM: Galliers Phone: 76429 MailCode: 510

ACTION PERF. GOAL DATE: 10-17-99 DATE CKLIST CMPLTD: 10-15-99

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

1. ACTION LETTER with supervisory signatures  
Are there any Phase 4 commitments? Ph4 CHM (NDA 61-065) AP ☒ AE ☐ NA ☒  
Yes ☐ No ☒
2. Have all disciplines completed their reviews?  
If no, what review(s) is/are still pending? Yes ☒ No ☐
3. LABELING (package insert and carton and container labels).  
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) Draft ☐  
Revised Draft ☒  
Final ☐
4. PATENT INFORMATION ☒
5. EXCLUSIVITY CHECKLIST ☒
6. PEDIATRIC PAGE ☒
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). ☒
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES  
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.  
If no audits were requested, include a memo explaining why.

9. REVIEWS & MEMORANDA:

|                                                                  |                                 |                                                                              |
|------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------|
| DIVISION DIRECTOR'S MEMO                                         | If more than 1 review for any   | <u>NONE</u>                                                                  |
| GROUP LEADER'S MEMO                                              | 1 discipline, separate reviews  | <input checked="" type="checkbox"/>                                          |
| MEDICAL REVIEW                                                   | with a sheet of colored paper.  | <input checked="" type="checkbox"/>                                          |
| SAFETY UPDATE REVIEW                                             | Any conflicts between reviews   | <input checked="" type="checkbox"/>                                          |
| STATISTICAL REVIEW                                               | must have resolution documented | <u>N 61-065</u>                                                              |
| BIOPHARMACEUTICS REVIEW                                          |                                 | <u>N 61-065</u>                                                              |
| PHARMACOLOGY REVIEW (Include pertinent IND reviews)              |                                 |                                                                              |
| Statistical Review of Carcinogenicity Study(ies)                 |                                 |                                                                              |
| CAC Report/Minutes                                               |                                 |                                                                              |
| CHEMISTRY REVIEW                                                 |                                 | <u>N 61-065</u>                                                              |
| Labeling and Nomenclature Committee Review Memorandum            |                                 | <input checked="" type="checkbox"/>                                          |
| Date EER completed _____ (attach signed form or CIRT's printout) |                                 | OK <input checked="" type="checkbox"/> No <input type="checkbox"/>           |
| FUR needed _____ FUR requested _____                             |                                 |                                                                              |
| Have the methods been validated?                                 |                                 | Yes (attach) <input type="checkbox"/> No <input checked="" type="checkbox"/> |
| Environmental Assessment Review / FONSI                          |                                 | Review <input type="checkbox"/> FONSI <input type="checkbox"/>               |

MICROBIOLOGY REVIEW

What is the status of the monograph?

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes ☒
11. MINUTES OF MEETINGS ☒  
Date of End-of-Phase 2 Meeting \_\_\_\_\_  
Date of pre-NDA Meeting \_\_\_\_\_ IND # \_\_\_\_\_
12. ADVISORY COMMITTEE MEETING MINUTES  
or, if not available, 48-Hour Info Alert or pertinent section of transcript. Minutes \_\_\_\_\_ Info Alert ☒  
Transcript \_\_\_\_\_ No mtg ☒
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS N/A
14. If approval letter, has ADVERTISING MATERIAL been reviewed?  
If no and this is an AP with draft labeling letter, has  
advertising material already been requested? Yes \_\_\_\_\_ No ☒  
Yes, documentation attached \_\_\_\_\_  
No, included in AP ltr ☒
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) ☒

# ACTION PACKAGE CHECKLIST

- Page 2 -

16. INTEGRATED SUMMARY OF SAFETY (from NDA)

✓

17. FDA LETTERS  
& MEMOS

✓

18. APPLICANT'S  
LETTERS

✓

19. CHARGE AND  
HISTORY CARD

✓

revision:1/16/98

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-102**

Additional Information for FemHrt may be found in  
FemHrt, NDA 21-065