

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-065

CORRESPONDENCE

M 527

Memorandum to the File

FEB 9 1999

To: NDA 21-065
From: Michael Ortwerth, Review Chemist [redacted] 2/8/99
Through: Moo-Jhong Rhee, Chemistry Team Leader [redacted] 2/8/99
Subject: Information Request for NDA 21-065 (Specification of Facility
Role as Drug Substance Supplier)
Date: 08-FEB-1999

A facility noted by the sponsor (Parke-Davis) is designated as a supplier of the drug substances Norethindrone acetate and Ethinyl estradiol. The designation of the facility as a supplier is unclear. The facility in question is ...



In order to determine the role of this facility, the sponsor (contact: Ms. Robin Pitts) was telephoned on 27-JAN-1999. Ms. Pitts informed me that the [redacted] is a third party that does not manufacture the drug substances. During this conversation, Ms. Pitts could not elaborate on the exact function of the facility.

On 29-JAN-1999, Mr. Len Lescosky (a CMC staff member for Parke-Davis) contacted me to inform me that [redacted] was an agent for [redacted] in the United States. Then, on 01-FEB-1999, Mr. Lescosky called to inform me that [redacted] accepts the drug substances and stores them before transfer to the Drug Product Manufacturer - Duramed.

On 01-FEB-1999, the Office of Compliance requested that I check with the sponsor to determine if [redacted] represented a name change for the company [redacted] is found in the Establishment Evaluation System to have the same mailing address as [redacted]. I contacted the sponsor on the same day to request the information and Mr. Lescosky returned my call to inform me that [redacted] is a holding company for both [redacted] and that [redacted] are sister companies.

At this time it is necessary to determine exactly what the function of the [redacted] site is in detail. Thus, an amendment to the NDA 21-065 should be submitted as soon as possible by the sponsor to address the following questions...

1. For what length of time are the drug substances stored at the [redacted] facility?
2. In what storage containers are the bulk drugs stored in during their time at the [redacted] facility?
3. What are the environmental conditions at the [redacted] facility and how are these conditions maintained?
4. What identification tests are performed on the drug substances before they are accepted for storage at the [redacted] facility?

cc: HFD-580/Division File (NDA 21-065)
HFD-580/MOrtwerth/MRhee/JMercier

Memo

NDA: 21-065
Drug Northindrone acetate/ethinyl estradiol
Sponsor: Parke-Davis
Date: 10/12/99

SAFETY UPDATE

For safety update see page 41 of Medical Officers review.

APPEARS THIS WAY
ON ORIGINAL

OCT 14 1999

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date:

From: David Hoberman, Ph.D., HFD-715

Subject: femhrt

File (NDA# 21-065)

There was one statistical issue arising at the last minute when the sponsor wished to have the

With respect to evaluating the effect of different doses of Femhrt on bone mineral density (BMD) in menopausal women, after several consults with the medical officer in HFD-510, Joanna Zawadski, M.D., we were satisfied that the sponsor had demonstrated highly statistically significant differences from placebo in BMD. The 1/5 dose resulted in an average positive change from baseline in BMD whereas the placebo patients declined on average.

There was an additional technical issue concerning a *post hoc* comparison of the 1/5 dose to the corresponding dose of unopposed estrogen. I explained that the p-value was essentially impossible to calculate, for there were a total of possibly 12 or 16 comparisons that had to be taken into account. Using Bonferroni corrections indicated that the *post hoc* p-value would be near .05, but it is impossible to determine whether the comparison could be regarded as "statistically significant." In addition, this treatment arm comparison seems to be of questionable relevance to the approval of femhrt.

APPEARS THIS WAY
ON ORIGINAL

OCT 14 1999

Group Leader Memorandum

NDA: 21-065

Drug: femhrt®
norethindrone acetate (NA)/ethinyl estradiol (EE) tablets

Proposed Doses: [redacted]
1.0 mg NA/5.0 mcg EE
[redacted]

Indications: Treatment of vasomotor symptoms associated with menopause
[redacted]
Protection against endometrial hyperplasia

Applicant: Parke Davis Pharmaceutical Research

Date Submitted: 12/17/98
Date of Review: 10/8/99

Group Leader: Marianne Mann, Deputy Director, HFD-580

Background

This NDA was submitted to support the approval of femhrt®, a combination estrogen/progestin tablet that contains ethinyl estradiol and norethindrone acetate. The applicant originally submitted [redacted] doses for consideration: [redacted] 1/5, [redacted] mg NA/mcg EE, respectively. During the NDA review process, however, the sponsor withdrew the [redacted]. The desired indications were:

- Treatment of moderate to severe vasomotor symptoms associated with menopause
- [redacted]
- [redacted]

Of note, NDA 21-102 was submitted concurrently to the Division of Endocrine and Metabolic Drug Products for the indication of:

- Prevention and management of osteoporosis.

Chemistry/Manufacturing

This product had a long history of chemistry and manufacturing difficulties (with manufacturing transfers from [redacted] to Duramed®) that delayed submission of an acceptable application. Thus, it is noteworthy that the clinical trials for this product were performed in the late 1980s and early 1990s, before our most recent guidance document for industry on hormone replacement therapy. There were no major chemistry issues raised during the review of this NDA and the product is considered acceptable for approval regarding Chemistry.

Product Name

The initially proposed name in 1994 by Parke Davis of [redacted] was found unacceptable due to "look alike, sound alike" to another product. The second name, proposed in 1996, was [redacted] and was found acceptable by the Labeling and Nomenclature Committee. The sponsor later submitted a revised request in 1996 for the name "FemHRT." A 1996 review by the Labeling and Nomenclature Committee found the

name "FemHRT" acceptable. During the current NDA review cycle, the sponsor modified the name "FemHRT" slightly to read "femHRT."

Concerns were raised during the review process that the name "femHRT" might be interpreted as "fem-heart" and inappropriately suggest cardiac benefit. These concerns led to reconsideration by the Labeling and Nomenclature Committee in September of 1999, and they found the name unacceptable. Their reasons included the concern about possible implied cardiac benefit, and that the name "femHRT" looked/sounded alike to two approved products "FemStat®" and [REDACTED]

After several teleconferences, FDA and the sponsor agreed to the name "femhrt" on October 6, 1999. It was agreed that all packaging, inserts, and promotional materials will be printed with the name "femhrt," with one exception: foil linings will be printed with the name "femHRT" for the initial 3-month supply of drug product. Thereafter, the sponsor has agreed to change the foil liners to read "femhrt" consistent with all other product packaging, inserts, and promotional material.

Preclinical Pharmacology and Toxicology

There were no significant toxicology issues raised, and the product was considered acceptable for approval from a pharmacology/toxicology perspective.

Biopharmaceutics

There were no significant biopharmacology issues raised, and the product was considered acceptable for approval.

Clinical Efficacy

Vasomotor Symptom Indication

The data to support the efficacy of FemHRT for the management of moderate to severe vasomotor symptoms in post-menopausal women demonstrated that all 3 doses of FemHRT were superior to placebo in reducing the frequency and severity of VMS after 12 weeks of treatment. There was evidence of dose-responsiveness regarding this treatment effect. The lowest dose of FemHRT, containing 2.5 mcg ethinyl estradiol, worked by week 6 with sustained efficacy through week 12. The mid and highest doses of FemHRT, containing 5.0 and 10.0 mcg ethinyl estradiol respectively, both worked by week 4 with sustained efficacy through week 12.

[REDACTED]

Endometrial Hyperplasia

The sponsor completed a 2-year controlled clinical trial assessing the effects of FemHRT on bone mineral density and also assessing the effects of FemHRT on endometrial hyperplasia. The trial included 9 treatment arms:

- Placebo
- 0.2 mg NA/1 ug EE versus 1 ug EE alone
- 0.5 mg NA/2.5 ug EE* versus 2.5 ug EE alone
- 1 mg NA/5 ug EE* versus 5 ug EE alone
- 1 mg NA/10 ug EE* versus 10 ug EE alone

With the exception of the 10 ug EE alone arm (prematurely discontinued due to a high rate of endometrial hyperplasia) all treatment arms completed enrollment. Follow-up biopsies at 12- months were obtained on between 75-82% of the fully enrolled treatment arms. At month 12, there were no cases of endometrial hyperplasia noted in the 3 FemHRT treatment arms. In contrast, there were 9 cases of hyperplasia in the 10 ug EE arm, 1 case in the 5 ug EE arm, and no cases in the 2.5 ug EE arm. At month 24, there were still no

cases of hyperplasia in the 3 FemHRT treatment arms, whereas there were a total of 10 cases in the 10 ug EE arm, 2 cases in the 5 ug EE arm, and 2 case in the 2.5 ug EE arm.

With the exception of the 10 ug EE alone arm, the rates of hyperplasia in the unopposed 2.5 ug and 5 ug EE arms were low. Additional data on endometrial biopsies, however, revealed that all unopposed EE arms had a greater rate of endometrial proliferation whereas the corresponding NA/EE arms had results more typical of a post-menopausal patient (atrophy or insufficient tissue). This data supports that the NA had a protective effect on the endometrium.

Clinical Safety

The critical safety issue in this review was whether the [redacted] of NA/EE had an acceptable safety profile given that it had [redacted]

The difference between the 1/5 and [redacted] is in the amount of EE present. This is the first combined product for hormone replacement therapy that proposes doses with [redacted] without a [redacted]. Additionally, one needs to consider that ethinyl estradiol is much more potent than other forms of estrogens, as shown in the following table (taken from the Textbook: *Treatment of the Postmenopausal Woman, Basic and Clinical Aspects*, Rogerio Lobo, Raven Press. 1994).

Relative Potency of Estrogen Preparations
Relative to Four Parameters* of Estrogenicity

Estrogen Preparation	Serum FSH	Serum CBG	Serum SHBG	Serum Angiotensin
Piperazine Estrone Sulfate ^a	1.1	1.0	1.0	1.0
Micronized Estradiol	1.3	1.9	1.0	0.7
Conjugated Estrogens	1.4	2.5	3.2	3.5
Diethylstilbestrol	3.8	70	28	13
Ethinyl Estradiol	(80-200)	(1000) ^b	614	232

*Based on FSH, follicle stimulating hormone; CBG, corticosteroid-binding globulin; SHBG, sex hormone-binding globulin.

^aUsed as a standard

^bEstimate in the absence of parallelism

A conservative estimate would suggest that if EE were 200 times more potent than conjugated estrogens, a dose of 5.0 mcg of EE correlates with 1.0 mg of conjugated estrogen and a dose of [redacted] EE correlates with [redacted] of conjugated estrogen. The highest dose of conjugated estrogen approved for combined hormone replacement therapy is 0.625 mg (in the products Prempro® and [redacted]). The dose of EE present in femhrt® [redacted] would correlate to [redacted] the approved 0.625 mg dose of conjugated estrogen.

Therefore, our reviews focused very closely on estrogen-related side effects (particularly those related to the endometrium). These included:

1. Endometrial Effects

Endometrial biopsies demonstrated no hyperplasia in either the 1/5 or 1/10 NA/EE treatment arms at month 12 or at month 24 of follow-up. Estrogen-related effects on the endometrium were nonetheless noted more frequently in the 1/10 arm versus the 1/5 arm. This conclusion was based on the following data from the 2-year study:

- The percentage of patients with vaginal bleeding or spotting was consistently greater in the 1/10 arm versus the 1/5 arm at month 3 (47% vs 38%), at month 6 (32% vs 24%), at month 12 (34% vs 24%) and at month 18 (27% vs 16%).
- The percentage of patients who withdrew due to unacceptable vaginal bleeding was greater in the 1/10 arm versus the 1/5 arm (5.5% vs 1.4%).

In addition, the shorter term 12-week study of vasomotor symptoms also demonstrated that the 1/10 dose had greater effects on the endometrium:

- The rates of bleeding and/or spotting at months 1, 2, and 3 were 13%, 16% and 12% in the 1/5 arm compared to 37%, 25% and 22% in the 1/10 arm.

2. Breast Cancer

A total of ten cases of breast cancer occurred during the total of four controlled clinical trials involving femhrt®. Three cases occurred in an unopposed EE arm: one each at 1 ug EE, 2.5 ug EE, and 10 ug EE. The remaining seven cases occurred in a femhrt® dosage arm: one at 0.2/1 NA/EE, one at 0.5/2.5, two at 1/5, one at 0.5/10, and two at 1/10. There is no evidence of dose-responsiveness regarding this particular adverse event, and it is unknown if estrogens (or progestins) increase the risk of breast cancer when taken long-term as hormone replacement therapy.

3. Thromboembolic events

A total of 6 of 1006 (0.6%) patients who received NA/EE had a thromboembolic event (deep vein thrombosis, thrombophlebitis, or stroke) during clinical trials compared to 2 of 562 (0.4%) EE patients and none of 247 placebo patients. The 6 cases involving femhrt® included: 1 case at the 1/20 dose (studied in a 1 year active controlled trial involving 87 women, 65 of whom received one of 5 doses of femhrt®), 2 cases at the 1/10 dose, 2 cases at the 1/5 dose and 1 case at .5/2.5 dose. While there is no evidence of dose responsiveness, thromboembolic events are known to occur in causal association to estrogen use and are more frequent at higher estrogen exposures. This fact supports the selection of a lowest effective dose of estrogen unless there is substantially greater benefit with a higher dose to offset this risk.

4. Gallbladder Disease

One patient in the 1/5 NA/EE arm and one patient in the 1/10 NA/EE arm experienced a gallbladder disorder (both considered serious adverse events). The limited number of gallbladder cases do not allow determination of dose-responsiveness between the 1/5 and 1/10 treatment arms. The known causal association of this event with estrogen, however, supports the selection of a lowest effective dose of EE unless there is a clinical need and benefit that is clearly demonstrated for a higher dose.

5. Overall Adverse Event Profile

The most frequent adverse events reported by femhrt® subjects in the long-term study-390 were headache and rhinitis, viral infection, nausea and vomiting, and breast pain. Of these, nausea and vomiting and breast pain occurred more frequently in the highest dose 1/10 dose arm. More specifically, nausea and vomiting occurred in 3%, 4.5%, and 7.7% of the 0.5/2.5, 1/5, and 1/10 treatment arms, respectively. Breast pain occurred in 3.0%, 0%, and 10.8% at each of the 3 increasing doses of femhrt®, respectively.

Conclusions:

No dose of femhrt® was studied specifically for the indication of treatment of [redacted] The small subset of patients who had symptoms of [redacted] and who received femhrt® does not substantiate the efficacy of the drug for this condition. I therefore do not recommend femhrt for approval for the treatment of [redacted]

Regarding vasomotor symptoms, the [redacted] of femhrt® offers no substantial benefit regarding efficacy could pose greater risk than the 1/5 dose. Therefore, I conclude that the [redacted] of femhrt® is unacceptable for approval. The 1/5 dose of femhrt® is safe and effective for the treatment of vasomotor symptoms and it also provides adequate long-term endometrial protection. Therefore, I find the 1/5 dose of

femhrt® acceptable for approval. Finally, although the sponsor has withdrawn
for consideration of approval,

/S/

Marianne Mann, Deputy Director, DRUDP

10/19/99

**APPEARS THIS WAY
ON ORIGINAL**



October 15, 1999

NDA 21-065

Ref. No. 024

femhrt™ (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Final Draft Labeling

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

We refer to our files for NDA 21-065 for femhrt 1/5. Enclosed are final draft versions of the Physician's Package Insert and the Information for Patients sheet.

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

Sincerely,

A handwritten signature in dark ink, appearing to read 'Ross Lobell'.

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
10-15-1999/RN-024/21-065/CI-0376/Letter

Attachment

59 Page(s) Redacted

Draft

Labeling



WORLDWIDE REGULATORY AFFAIRS

Sending Fax Number: (734) 622-3283

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- 3767*

PAGE 1 OF 32

TO: Dr. D. Davis / Dianne Moore

FAX #: 301-827-4267

FROM: Ross Labell

DATE: 10/15/99

Final Draft Labeling

NDA 21-065

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.

30 Page(s) Redacted

Draft

Labeling

NDA 21-065

Food and Drug Administration
Rockville MD 20857

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

AUG 31 1999

Dear Ms. Taylor:

Please refer to your pending December 16, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FemHRT (norethindrone acetate and ethinyl estradiol) [redacted] 1mg/5mcg, [redacted]

We have completed our review of the Chemistry section of your submission and have the following comments and information requests:

1. Please submit a Letter of Authorization to support cross-reference to [redacted] Type I DMF.
2. Please establish and perform acceptance testing for the drug substances norethindrone acetate and ethinyl estradiol in accordance with the drug substance supplier release specifications. All drug substance batches received by the drug product manufacturer, Duramed, outside of these established specifications should not be accepted for manufacturing.

4. Please explain standard operating procedures for investigations carried out in the case of out-of-specification results found in [redacted] assays during drug product manufacturing including any reprocessing operations.
5. Friability testing is presented in the Master Batch Records for the drug product manufacturer, Duramed, yet is not presented as an in-process control in the body of the NDA. Please add friability testing to the in-process control tests unless its omission is justified.

6. After [redacted] during drug product manufacturing, in-process controls should include tests and specifications for [redacted] content.
7. Please clarify as to whether drug product reprocessing operations are being implemented. If not, please state so.
8. Please provide sampling procedures for the drug products.
9. Please revise the specifications for the drug product as follows:

For Norethindrone acetate (NA):

Please identify and qualify all unknown impurities peaks that appear at values of >0.5% for the 1 mg NA tablets.

For Ethinyl estradiol (EE):

Suggested Revisions are:

Specification	Current	Suggested Revision	Comment
Assay EE (Shelf-Life)	[redacted]	[redacted]	To account for impurity limits.
Assay EE (Release)			To account for impurity limits.
EE Deg./Imp.			
[redacted]	[redacted]	[redacted]	Based on presented data.
[redacted]			Based on presented data.
Total Other Unknown			Based on presented data.
Total Imp./Unk.			Based on presented data.

10. The Specifications and Test Methods for the Drug Product (Appendix 8; NDA Vol. 1.17) and the Methods Validation Package (Appendix 1- 7; NDA Vol. 1.21) are not properly edited and this creates confusion in review. Please resubmit these sections of the NDA in triplicate with corrections.
11. The Storage Statement for the drug product in Physician and Patient Package Inserts should be corrected and should read "Store at 25°C (77°F): Excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]"

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug
Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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] 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

**APPEARS THIS WAY
ON ORIGINAL**

Drafted by:emg/7.7.99

ACKNOWLEDGEMENT (AC)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 21-065

Food and Drug Administration
Rockville MD 20857

DEC 28 1998

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

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 (ethinyl estradiol/norethindrone acetate) Tablets

Therapeutic Classification: Standard (S)

Date of Application: December 16, 1998

Date of Receipt: December 17, 1998

Our Reference Number: 21-065

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 15, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 17, 1999 and the secondary user fee goal date will be December 17, 1999.

Please cite the 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/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Page 2

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic-Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE
NEW CORRESP

PARKE-DAVIS

October 15, 1999

NDA 21-065

Ref. No. 024

femhrt™ (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Final Draft Labeling

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

We refer to our files for NDA 21-065 for femhrt 1/5. Enclosed are final draft versions of the Physician's Package Insert and the Information for Patients sheet.

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

Sincerely,

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
10-15-1999\RN-024\21-065\CI-0376\Leter

Attachment

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

ARKE-DAVIS

October 14, 1999

32
ORIG AMENDMENT

BEST POSSIBLE COPY

NDA 21-065

Ref. No. 023

femhrt™ (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Hard Copy of September 15, 1999
E-mail

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

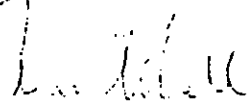
Dear Dr. Rarick:

We refer to our files for NDA 21-065, femhrt™ (norethindrone acetate and ethinyl estradiol) Tablets, and Ms. Spell-LeSane's request to provide a paper copy of our September 15, 1999 secure E-mail. This E-mail provided additional information requested by the Agency during our September 10, 1999 telephone meeting regarding labeling.

A copy of this secure E-mail is attached.

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

Sincerely,


Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL: kb-

10-14-1999 RN-023/21-065/CI-0376/Lener
Attachment

Ⓟ PARKE-DAVIS

DUPLICATE
NEW COPIES

October 13, 1999

NDA 21-065

Ref. No. 022

femhrt™ (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Response to FDA Questions

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

We refer to our files for NDA 21-065, femhrt™ (norethindrone acetate and ethinyl estradiol) Tablets, and to the October 13, 1999 request from Ms. Dornette Spell-LeSane to provide confirmation that all primary and secondary labeling will include lot and expiration dating. In addition to this request, Ms. Spell-LeSane also requested clarification of Item 3 in our memo of understanding dated October 8, 1999.

We confirm that all primary and secondary labeling for femhrt will contain both lot and expiration dating.

With regard to Item 3 of the October 8, 1999 memo of understanding for our October 6, 1999 telephone meeting to discuss the tradename for this product, Item 3 should read:

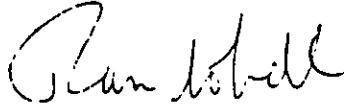
3. Primary packaging – foil blisters and foil pouches – will be launched with the originally submitted tradename – FemHRT – until supplies are exhausted in March of 2000. At this time, these packaging pieces will also be changed to the new tradename (femhrt).

APPEARS THIS WAY
ON ORIGINAL

Lisa Rarick, M.D.
NDA 21-065
October 13, 1999
Page 2

Should there be any questions regarding this submission, please feel free to contact me at 734/622-2111 or send a facsimile to 734/622-3283.

Sincerely,

A handwritten signature in cursive script, appearing to read "Ross Lobell".

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb

10-13-1999.RN-022\21-065\CI-0376\Letter

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

PARKE-DAVIS

October 12, 1999

ORIG AMENDMENT

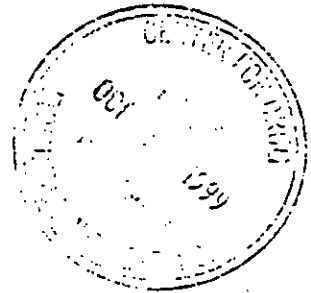
NDA 21-065

Ref. No. 021

femhrTM (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Response to September 30, 1999
Agency Questions

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

We refer to our files for NDA 21-065, femhrTM (norethindrone acetate and ethinyl estradiol) Tablets, and to the set of questions provided by Ms. Dornette Spell-LeSane, via secure E-mail on September 30, 1999.

Attached are our responses to each question. Please note that this response was also provided via secure E-mail to Ms. Spell-LeSane on October 4, 1999.

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

Sincerely,

A handwritten signature in cursive script that reads "Ross Lobell".

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb

10-12-1999 RN-021\21-065\CI-0376\Letter

Attachment



October 12, 1999

NDA 21-065

Ref. No. 020

*femhrt*TM (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Draft Labeling with Revised Trademark

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

We refer to our files for NDA 21-065, *femhrt*TM (norethindrone acetate and ethinyl estradiol) Tablets, and to our telephone meeting of October 6, 1999, wherein agreement was reached regarding a revised trademark. The agreed upon trademark consists of all lower case letters of equal prominence - *femhrt*.

In addition, during this meeting it was further agreed that Parke-Davis would revise secondary packaging to incorporate the revised trademark. Draft versions of this labeling for both professional samples and marketed product are enclosed:

Bottle Packages:

- *femhrt* 1/5 bottle label 0144G031
- *femhrt* 1/5 carton label 0144C041



Lisa Rarick, M.D.
NDA 21-065
October 12, 1999
Page 2

Blister Card Secondary Packages:

- 28 count blister card carton for femhrt 1/5 0144C011

- [Redacted]

- [Redacted]

Blister Card Early Experience Samples (28 count):

- femhrt 1/5 carton 0144C051
- femhrt 1/5 dealer container 0144C061

- [Redacted]

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

Sincerely,



Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
10-12-1999\RN-020\21-065\CI-0376\Letter

Attachments

APPEARS THIS WAY
ON ORIGINAL.

PARKE-DAVIS

Sean Brennan, Ph.D.

October 8, 1999

Ref. No. 018

ORIG. AMEND. SUBMIT

NDA 21-065

femhrt™ (norethindrone acetate and ethinyl
estradiol) Tablets

Re: Response to FDA Questions (CMC)

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Please refer to our NDA 21-065, femhrt™ (norethindrone acetate and ethinyl estradiol) tablets and the conversation between Ross Lobell of Parke-Davis and Dornette Spell-LeSane of your office on October 4, 1999.

We agree to revise our dissolution specification for both norethindrone acetate and ethinyl estradiol to not less than (Q) of the label claim dissolved in minutes.

If you have any questions regarding this submission, please contact me at 734/622-7596 or Len Lescosky at 734/622-7196, or send a facsimile to 734/622-7890.

Sincerely,

Sean Brennan

Sean Brennan, Ph.D.
Vice President, CMC
Worldwide Regulatory Affairs

SB:kb

10-08-1999:RN-018\21-065\CI-0376\Lener

 **PARKE-DAVIS**

October 8, 1999

NEW CORREL

NDA 21-065
Ref. No. 017
FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: October 1997 Lancet Article

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

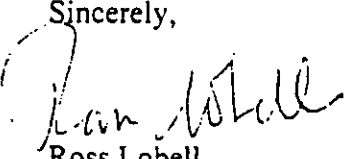
We refer to our files for NDA 21-065 for FemHRT™ (norethindrone acetate and ethinyl estradiol) Tablets and to our telephone conference of September 17, 1999, wherein we discussed the possible impact of the October 1997 Lancet article on breast cancer associated with HRT.

A copy of this article is enclosed.

We hereby request a copy of the Agency's position regarding the possible impact of the data presented in this study, and upon the current FDA recommended class labeling language regarding the relative risk of breast cancer associated with HRT use.

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

Sincerely,


Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
10-08-1999/RN-017/21-065/CI-0376/Lener

October 8, 1999

NDA 21-065

Ref. No. 016

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Memo of Understanding for
October 6, 1999 Telephone Conference

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

We refer to our files for NDA 21-065 for femhrt and to our telephone conference held on October 6, 1999. The following is our understanding of this conference.

Present from FDA: John Jenkins, MD, ODE2, Office Director; Florence Houn, MD, Office Director, ODE3; Marriane Mann, MD, Deputy Director, DRUDP; Norman Drezin, RPHJD, Acting Director, DDMAC; Michael Ortwerth, PhD, Chemistry Reviewer; Moo-Jhong Rhee, PhD, Chemistry Team Leader; Lisa Stockbridge, PhD, Regulatory Review Officer, DDMAC; Terri Rumble, BSN, Chief Project Management Staff, DRUDP; and Dornette Spell-LeSane, Consumer Safety Officer, DRUDP.

Present from Parke-Davis: Bill Merino, Regulatory Affairs; Byron Scott, Regulatory Affairs; Stuart Kolinsky, Regulatory Affairs; Randall Whitcomb, Drug Development; Fred Hershenson, Drug Development; Ross Lobell, Regulatory Affairs.

The object of the meeting was to discuss and reach agreement regarding labeling materials for the initial launch of the femhrt product as well as establish timing for the change-over to the new trade name - femhrt.

Lisa Rarick, M.D.
NDA 21-065
October 8, 1999
Page 2

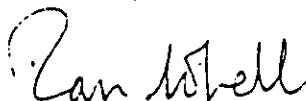
APPEARS THIS WAY
ON ORIGINAL

Agreements reached:

1. All promotional materials, including launch materials will utilize the new trade name - femhrt. No DTC campaigns are planned at present.
2. All secondary packaging materials will be changed to the new trade name at launch. This includes boxes and cartons.
3. Primary packaging - foil blisters and foil pouches - will be launched with the originally submitted trade name - femhrt - until supplies are exhausted in March of 2000. At this time these packaging pieces will also be changed to the new trade name (femhrt).
4. Parke-Davis will provide revised draft labeling of the secondary packaging to FDA prior to the PDUFA action date of October 17, 1999.
5. FDA will include agreements 1, 2, and 3 in the action letter for this product.
6. Based on a telephone discussion with Dornette Spell-LeSane on October 7, 1999, we will also utilize the FDA recommended storage statement for this product on the secondary packaging to be used for product launch.

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

Sincerely,



Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb

10-08-1999\RN-016\21-065\CI-0376\Lener

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

NEW CORRESP

PARKE-DAVIS

October 1, 1999

11C

Sean Brennan, Ph.D.

Ref. No. 014

NDA 21-065

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Response to FDA Questions (CMC)

Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic

Drug Products (HFD-580)

Document Control Room 12B45

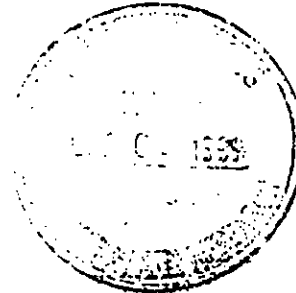
Office of Drug Evaluation II

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane

Rockville, Maryland 20857



Dear Dr. Rarick,

Please refer to our NDA 21-065, FemHRT (norethindrone acetate and ethinyl estradiol) tablets and the teleconference today between Dr. Moo-Jhong Rhee, Dr. Michael Ortwerth, and Ms. Dornette Spell-Lesane of the FDA, and Dr. Sean Brennan, Dr. Phil Simonson, and Mr. Len-Lescosky of Parke-Davis. At this meeting, the Parke-Davis and FDA reached the following agreements:

- FDA accepts our commitment to tighten the norethindrone acetate API assay specification to the [redacted] internal limit of [redacted]
- As a Phase 4 commitment, within the first year, post approval, we will [redacted]
- An 18-month shelf life is accepted for the product based on analysis of the NDA stability batches manufactured at Duramed. Expiration dating will not be extended based on these batches until full term data is obtained on [redacted] batches of each strength and package. This data will be submitted to the FDA as a prior approval supplement.

If you have any questions regarding this submission, please contact me at 734/622-7596, send a facsimile to 734/622-7890, or contact Len Lescosky at 734/622-7196.

Sincerely,

Sean Brennan
Sean Brennan

SB:ab

10-10-1999 RN-014 21-065 CI-0376



Sean Brennan, Ph.D.
Vice President
Worldwide Regulatory Affairs

September 29, 1999

DUPLICATE

ORIGINAL AMENDMENT

BC

Ref. No. 013

NDA 21-065

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Response to FDA Questions (CMC)

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Please refer to our NDA 21-065, FemHRT (norethindrone acetate and ethinyl estradiol) tablets. Responses were submitted on September 17, 1999 to questions from Dr. Moo-Jhong Rhee (DNDC II) dated August 27, 1999 on the Chemistry, Manufacturing and Controls section of our application. On September 27, 1999, a meeting was held between Dr. Moo-Jhong Rhee, Dr. Michael Ortwerth, and Ms. Diane Moore of the FDA, and Dr. Sean Brennan, Dr. Phil Simonson, and Mr. Len Lescosky of Parke-Davis to discuss our responses and additional comments from Dr. Ortwerth.

At this meeting, the following bolded comments and/or requests were made by FDA. Our responses to these items are provided following each item as necessary.

1. The upper limit content uniformity specification of proposed in our July 20, 1999 letter was accepted.
2. The assay specification for norethindrone acetate API should be tightened to match the release limit.

The assay specification will be tightened to for norethindrone acetate API.

3. The residual alcohol test and specification for tablet release is acceptable.

[REDACTED]

4. If the [REDACTED] then the specifications proposed in our response are acceptable.

Our commitment to establish a release limit of [REDACTED] % for ethinyl estradiol (EE) and tighten the compliance limit to [REDACTED] % assumed that the expiry period for the product would be [REDACTED] months as stated in the NDA. The USP monograph for combination NA/EE tablets specifies an assay limit of [REDACTED] to [REDACTED] % for ethinyl estradiol. As discussed below, our analysis of the stability data from both [REDACTED] and Duramed show that the product meets or will meet assay specifications for ethinyl estradiol through at least 18 months with a lower assay limit of [REDACTED] % when the data is corrected for any overages used in the manufacture of the tablet. Applying the monograph limit of [REDACTED] as used for our other NA/EE combination tablet products (Loestrin and Estrostep), a longer expiry period should be considered.

Once we agree on the assessment of the stability data, a lower compliance limit for assay can be established.

5. Based on FDA's review of the stability data, a [REDACTED] month expiry period is recommended.

We have reanalyzed the stability data from [REDACTED] and Duramed after correcting the assay results for the overage of EE used in the manufacture of tablets by subtracting the overage from the assay result. Based on these analyses, an expiration period of 18 months is appropriate.

For the [REDACTED] data:

- A lower specification of [REDACTED] was used.
- Linear regression lines and confidence bands were obtained for each individual lot * package configuration. Data was not pooled.
- Confidence bands for individual values, which are more conservative than those based on the mean, were used. A two-sided 90% confidence band (5% in the upper and lower, respectively) is used.

In the [redacted], there is no batch where the lower confidence limit intersects [redacted] specification limit at 18 months. Since this analysis is based on worst case loss in EE assay (after removal of the overage) and conservative estimates of uncertainty (confidence bands based on individual values and no pooling of data) were used, a shelf life of 18 months based on these data is appropriate.

For those lots produced at Duramed:

- Data for all nine batches was pooled (slope/intercept homogeneity); six batches had 9 months and 3 had 12 months storage.
- Data are plotted using a [redacted] one-sided confidence band for mean ethinyl estradiol assay (corrected for the 2% overage).

In the attached plot labeled "FemHRT Duramed Data (12 Month on 3 Lots)", the estimated shelf life, assuming a common slope/intercept model was about 21 months.

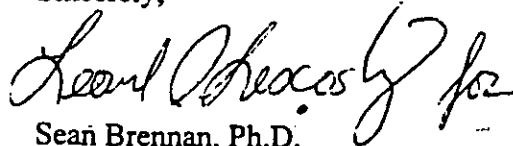
6. FDA requested a commitment that the expiry period be extended on the basis of real time data on post-approval commercial lots.

Since the NDA stability batches produced at Duramed were by the same process with the same equipment as that intended for commercial production, the expiration period may be extended on the data from these batches when the correction for the overage is applied. Expiration dating would not be extended until full term data on these batches is obtained on three batches of each strength and package.

7. All other responses in our September 17, 1999 letter were adequate

If you have additional questions or comments on these responses, we would like to meet with your staff in person. I look forward to hearing from you. If you have any questions regarding this submission, please contact me at 734/622-7596 or via FAX at 734/622-7890, or Len Lescosky at 734/622-7196.

Sincerely,



Sean Brennan, Ph.D.

 **PARKE-DAVIS**

September 28, 1999

NDA 21-065
FemHRT

Re: FAX of Package Labels

Dorsette Spell-LeSane
Division of Reproductive and
Urologic Drug Products (HFD-580)
Document Control Room 17B45
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Spell-LeSane:

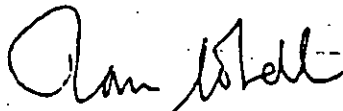
We refer to our files for FemHRT and to NDA numbers 21-065 and 21-102. Per your request are the package labels for FemHRT 1/5

A hard copy of each of these labels will be provided in a separate letter to be sent Federal Express.

Please note that this FAX has been provided to both DMEDP and DRUDP and that a hard copy of the labels will also be provided to both divisions.

Should you have any questions regarding this FAX please call me at 734/622-2111 or FAX me at 734/622-3283.

Sincerely,



Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
09-28-1999/21-065/CI-0376/Letter

Attachments

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical
Research

2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

ORIGINAL

NEW CORRESP

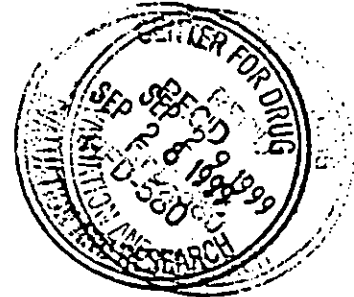
 **PARKE-DAVIS**

September 28, 1999 *NC*

NDA 21-065
Ref. No. 012
FemHRT

Re: 


Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

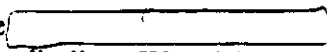




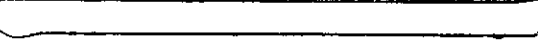
Dear Dr. Rarick:

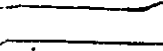
We refer to our files for FemHRT and to NDAs 21-065 and 21-102.

Due to the current 

 we have
decided to discontinue pursuing its registration at this time.

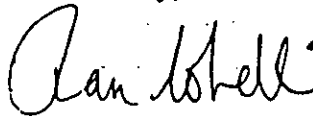
Therefore, we request that the  be withdrawn from both NDA 21-065 and 21-102 without prejudice. We wish to continue ongoing registration activities for the FemHRT 1/5  tablet strengths and look forward to the completion of the Agency's review of these  dose strengths.

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

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

Please call either Mr. Ross Lobell at 734/622-2111 or Ms. Mary Taylor at 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

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

RL:kb 09-28-1999\RN-012\21-065\CI-0376\Letter
Division of Warner-Lambert Company

® PARKE-DAVIS

September 17, 1999

ORIGINAL
ORIGINAL AMENDMENT
SL

Ref. No. 011

NDA 21-065

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Response to FDA Questions (CMC)

Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic

Drug Products (HFD-580)

Document Control Room 12B45

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane

Rockville, Maryland 20857



Dear Dr. Rarick:

Reference is made to our pending NDA 21-065 for FemHRT™ (norethindrone acetate and ethinyl estradiol) Tablets and the letter sent by Moo-Jhong Rhee of your office on August 27, 1999. Following is a list of the FDA's questions/comments in italics followed by our response.

1. *Please submit a Letter of Authorization to support cross-reference to [redacted] Type I DMF.*

A Letter of Authorization allowing cross-reference to [redacted] Type I DMF is provided in Attachment 1.

2. *Please establish and perform acceptance testing for the drug substances norethindrone acetate and ethinyl estradiol in accordance with the drug substance supplier release specifications. All drug substance batches received by the drug product manufacturer, Duramed, outside of these established specifications should not be accepted for manufacturing.*

Future receipts of drug substance will be tested and released according to the USP methods and specifications at the Duramed facility.

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

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

Lisa Rarick, M.D.
NDA 21-065
September 17, 1999
Page 8

11. *The Storage Statement for the drug product in Physician and Patient Package Inserts should be corrected and should read "Store at 25 °C (77 °F): Excursions permitted to 15-30 °C (59-86 °F) [See USP Controlled Room Temperature]"*

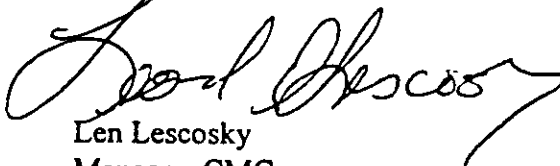
Since the package insert has not yet been printed, storage conditions listed on this component will be changed to the statement from the stability guidance requested above. Other packaging components, however, have already been printed with the statement "Store at controlled room temperature (20-25°C)". These materials were ordered so we could manufacture our validation batches, which we expect to use as our first commercial batches. Typically, new packaging components are available for use four months after ordering the materials. Revising the storage statement would significantly delay the launch of our product.

As discussed at our September 10, 1999 teleconference, we will use the "Store at controlled room temperature (20-25°C)" statement on the labeling for the first commercial batches. We commit to order new labels using the recommended statement for further batches on confirmation from the FDA that the proposed labels are acceptable.

As discussed at the September 10, 1999 teleconference, we will add to the Physician and Patient Package Inserts a statement that FemHRT is distributed by Parke-Davis.

If you should have any questions regarding this submission, please contact me at 734/622-7196 or Sean Brennan at 734/622-7596, or via FAX at 734/622-7890.

Sincerely,



Len Lescosky
Manager, CMC
Worldwide Regulatory Affairs

LL:kb
09-17-1999\RN-011\21-065\CI-0376\Letter

Attachments

REVIEWS COMPLETED

CSC ACTION

☐ LETTER ☐ MAIL ☐ MEMO

CSC INITIALS DATE

Pharmaceutical
Research

2000 Pymouth Road Phone (734) 622-7000
Ann Arbor, MI
48106

ORIGINAL
ORIG AMENDMENT
BB-

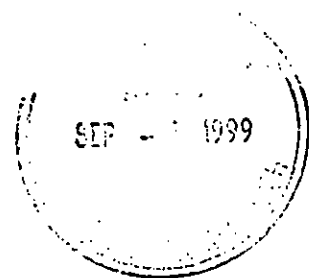
LAKE-DAVIS

August 31, 1999

NDA 21-065
Ref. No. 009
FemHRT

Re: Request for Additional 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:

Reference is made to our files for NDA 21-065 for FemHRT and to our telephone conversation with Ms. Dornette Spell-Lesane and Dr. Venkateswa Jarugula, wherein a request was made to provide the non-mem files for our population pharmacokinetics study (RR 720-03946).

These files are enclosed. As requested, each of the 6 files (3 input files and 3 data files) have been named separately and are in ASCII format.

This disk has been scanned for viruses using Network Associates Inc. VirusScan NT v. 4.0.2.

Should you have any questions regarding this submission please contact me at 734/622-2111 or FAX me at 734/622-3283

Sincerely,

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

RL:kb
08-31-1999\RN-009\21-065\CI-0376\Letter
Attachment

Desk Copy: Dr. Venkateswa Jarugula (HFD-870)

REVIEWS COMPLETED

ORIGINAL
NEW CORRESP
NV

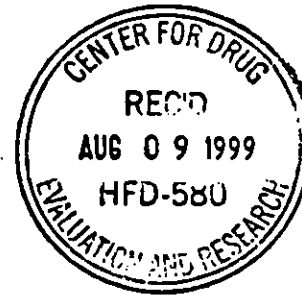
PARKE-DAVIS

August 6, 1999

NDA 21-065
Ref. No. 008
FemHRT

Re: Electronic Copies

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

We refer to our files for FemHRT, NDA 21-065 and to our August 2, 1999 telephone conversation with Ms. Dornette Spell-Lesane, wherein she requested that electronic files of The Integrated Summary Of Safety from the original NDA be provided as electronic files in WORD 7.0 format or lower.

This file is contained on the enclosed diskette and have been scanned with Network Associates VirusScan. Specifically this diskette contains NDA Volume 1.50 ISS pages 1-57. This file is in Microsoft WORD v. 7.0.

If there are questions regarding this submission please call me at 734\622-2111 or via FAX at 734\622-3283.

Sincerely,

Ross Lobell
Senior Manager
Worldwide Regulatory Affairs

3/16 OK - copy made

RL:kb
08-06-1999\RN-008\21-065\CI-0376\Letter

Attachment

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

Handwritten: /S/ 8/16/99

 **PARKE-DAVIS**

July 20, 1999

DUPLICATE
ORIG AMENDMENT

NDA 21-065

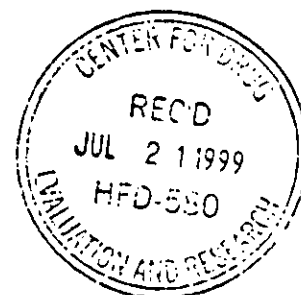
Ref. No. 006

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Amendment to NDA

Sean Brennan, Ph.D.

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Reference is made to our NDA 21-065 for FemHRT™ (norethindrone acetate and ethinyl estradiol) Tablets. We have discussed the specifications for the Content Uniformity of the tablets with Dr Michael Ortwerth of your Division. Based on these discussions we propose to change the Content Uniformity specifications as follows:

Norethindrone acetate: Meets USP requirements for compressed tablets.

Ethinyl estradiol (EE): Ten units are tested. The requirements are met if the amount of EE in each of the 10 dosage units is within the range of 85% to 115% of the label claim and the relative standard deviation of the 10 units is less than or equal to 6.0%. If one unit is outside the range of 85% to 115% of the label claim and no unit is outside the range of 75% to 140% or if the relative standard deviation is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than one unit of the 30 is outside the range of 85% to 115% of the label claim and no unit is outside the range of 75% to 140% of the label claim, and the relative standard deviation of the 30 dosage units does not exceed 7.8%.

If you have any questions or comments please contact me at 734/622-7596 or by FAX at 734-622-7890.

Sincerely,

Sean Brennan

Sean Brennan

SB:dp

07-20-1999 RN-006 21-065\CF-0376\Letter

PARKE-DAVIS

BEST POSSIBLE COPY

June 24, 1999

Ref. No. 005

NDA 21-065

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

ORIGINAL

ORIG AMENDMENT

/S/

Re: Amendment to NDA

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Reference is made to our pending NDA 21-065 for FemHRT™ (norethindrone acetate and ethinyl estradiol) Tablets.

This NDA Amendment contains updated stability data (24 months) for batches of FemHRT Tablets manufactured at the [] facility in []. The stability studies are included in Attachment 1. Statistical analyses for these studies are included in Attachment 2. No out of specification results were observed. The stability data supports the [] month expiration period requested.

During the 18 months stability sample testing, the run time was extended for the assay method to quantitate a late [] observed in the ethinyl estradiol (EE) [] at a relative retention time of about []. If present, this unknown was included in the stability tables in the "Total Other Unknown" column under EE degradation products at the 18 month test interval in the original NDA submission. This peak, seen in the [] used for EE assay, was subsequently identified as [] a degradation product of norethindrone acetate (NA). A memo regarding the isolation and identification of this degradation product is included in Attachment 3.

/S/ 11/17/99

/S/ See (1) memo of 11/17/99 call #2

Lisa Rarick, M.D.
NDA 21-065
June 24, 1999
Page 2

In this amendment, for appropriate presentation, the 18-month stability data has been revised to report this peak as a degradation product of NA. The value obtained for [] in the [] has been calculated as a percentage of NA. The calculated value is included in the "Total Other Unknowns" column in the degradation products tabulation for NA. When the values in the column "Total Other Unknowns" include other unknown peaks, the amount of [] is reported in a footnote.

[] is observed at no more than []% of NA label claim through 24 months storage at 25°C/ 60% RH. The amount of this impurity seen in stability samples is low. When seen and reported as a total other unknown, no specification is necessary for this impurity.

Should you have questions regarding this submission, please contact me at 734/622-5781 or via FAX at 734/622-7890 or Dr. Sean Brennan at 734/622-7596.

Sincerely,



Philip G. Simonson, Ph.D.
Director, CMC
Worldwide Regulatory Affairs

PS\dp
06-24-1999\RN-00521-065\CI-0376\Letter

Attachments

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

APPEARS THIS WAY
ON ORIGINAL

® PARKE-DAVIS

June 7, 1999

ORIGINAL

ORIG AMENDMENT

BEST POSSIBLE COPY

NDA 21-065

Ref. No. 004

FemHRT® (norethindrone acetate and
ethinyl estradiol tablets)

Re: Amendment to Pending Application

Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic
Drug Products (HFD-580)

Document Control Room 12B45

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane

Rockville, Maryland 20857

Dear Dr. Rarick:



Reference is made to our pending NDA 21-065 for FemHRT® Tablets (norethindrone acetate and ethinyl estradiol tablets). Reference is also made to the conversation on May 21, 1999 between Dr. Michael Ortworth of your division and Ms. Robin Pitts of Parke-Davis.

[redacted] the manufacturer of child resistant closures for the 90 count bottles of FemHRT Tablets, has withdrawn the Drug Master File No. [redacted]. The DMF has been resubmitted by [redacted] as DMF No. [redacted]. A letter authorizing referral to the DMF is attached.

Should you have questions regarding this submission, please contact me at 734/622-5781 or via FAX at 734/622-7890 or Dr. Sean Brennan at 734/622-7596.

Sincerely,

Philip G. Simonson, Ph.D.

Director, CMC

Worldwide Regulatory Affairs

PS dp

06/07/1999 RN-004 21-065 CI-0376 Letter

Attachment

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

® PARKE-DAVIS

ORIGINAL

ORIG AMENDMENT

SV

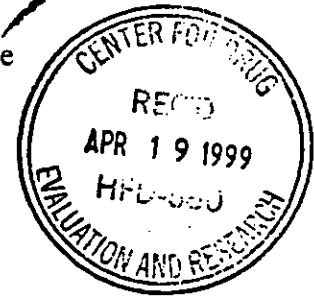
April 15, 1999

NDA 21-065

Ref. No. 003

FemHRT™ (norethindrone acetate and
ethinyl estradiol) Tablets

Re: Four-Month Safety Update



Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic

Drug Products (HFD-580)

Document Control Room 12B45

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane

Rockville, Maryland 20857

Dear Dr. Rarick:

Pursuant to 21 CFR§314.50(d)(5)(vi), enclosed is the Four-Month Safety Update for the New Drug Application 21-065 for FemHRT™ (norethindrone acetate and ethinyl estradiol tablets) submitted on December 17, 1998. The 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]

[redacted] and prevention of osteoporosis. Included in the NDA were 4 clinical trials (376-343, -359, -368, and -390). At the time of submission, one FemHRT study (376-401) was ongoing, and since the submission, one additional FemHRT study was initiated (376-408).

This update contains new safety information that was not included in the NDA, which includes serious adverse events and withdrawals due to adverse events that have occurred in Studies 376-401 and 376-408.

In accordance with the January 1999 "Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs," we have submitted an electronic archive that contains the following:

5/3 Review
pending
151

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> FINAL
151 5/4/99	
CSO INITIALS	DATE

Lisa Rarick, M.D.

NDA 21-065

April 15, 1999

Page 2

- Archive Table of Contents
- New patient CRFs, with bookmarks, links, and annotations for withdrawals due to an adverse event
- Cover Letter
- FDA Form 356h

A description of the electronic archive of the FemHRT Safety Update Electronic Archive is attached.

If there are any questions, please feel free to contact me at 734/622-5000 or Ms. Robin Pitts at 734-622-5628 or via FAX at 734/322-3283.

Sincerely,



Mary E. Taylor
Director
Worldwide Regulatory Affairs

MT\dp

04-15-1999\RN-003\21-065\CI-0376\Letter

Attachments

Pharmaceutical
Research

2600 Plymouth Road Phone (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

March 30, 1999

NDA 21-065

Ref. No. 002

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

Re: Waiver of Patient CRFs for 4-Month
Safety Update

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 12B45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

BEST POSSIBLE COPY

Dear Dr. Rarick:

Pursuant to 505(b)(1) of the FDC Act, a new drug application (21-065) for FemHRT™ (norethindrone acetate and ethinyl estradiol tablets, USP) was submitted on December 16, 1998. The 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.

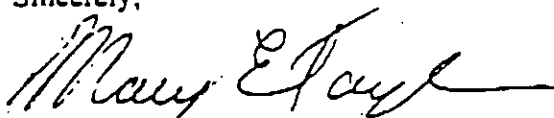
Reference is also made to a telephone conversation between Ms. Dornette Spell-Lesane of your Division and Ms. Robin Pitts of Parke-Davis on March 30, 1999 regarding a waiver of case report forms (CRFs) for patients who withdraw due to adverse events for the 4-Month Safety Update in Protocol 376-401 entitled, "A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel Group, Multicenter Study Assessing the Safety and Protective Effect on the Endometrium of 4 Dosage combinations of Norethindrone Acetate Plus Ethinyl Estradiol." Study 376-401 was initiated in February 1998 and the study is still blinded. The planned completion date for this study is 4th Quarter 1999. During that conversation, Ms. Spell-Lesane informed Ms. Pitts that Parke-Davis could submit a request to waive the requirement to submit CRFs.

In accordance with 21 CFR 312.50, we would like to request a waiver of the requirement to submit case report forms for each patient who did not complete Study 376-401 due to an adverse event.

Lisa Rarick, M.D.
NDA 21-065
March 30, 1999
Page 2

Since we plan to submit the 4-month Safety update on April 15, 1999, we would appreciate the Agency's response to this request before the due date. If there are any questions, please feel free to contact me at 734/622-5000 or Ms. Robin Pitts at 734-622-5628 or via FAX at 734/322-3283.

Sincerely,

A handwritten signature in cursive script, appearing to read "Mary E. Taylor".

Mary E. Taylor, M.P.H.

Director

Worldwide Regulatory Affairs

MT:dp

03-30-1999\RN-002\21-065\CI-0376\Letter

APPEARS THIS WAY
ON ORIGINAL

Pharmaceutical
Research

2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

 **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

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 24-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

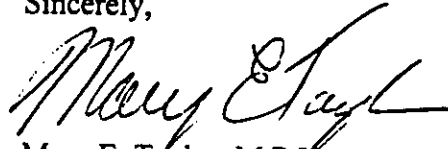
In addition to the User Fee Cover Sheet (Item 18), Patent and Exclusivity information (Item 13), Debarment Certification (Item 16), and the Field Copy Certification (Item 17) are located in Volume 1. Please refer to the attached Form FDA 356h and the NDA Index which detail the complete contents of this 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 DME 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

t:\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

Teleconference Minutes

OCT 29 1999

Date: October 6, 1999

Time: 2:25-3:00 p.m. Location: Parklawn; 17B43

NDA 21-065

Drug: femhrt (northindrone acetate/ethinyl estradiol)

Indication: Relief of vasomotor symptoms, Prevention of osteoporosis

Type of Meeting: Labeling Guidance

Meeting Chair: Florence Houn

External Lead: Ross Lobell

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

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

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

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Norman Drezin, RPh, J.D., Acting Director Division of Drug Marketing and Communication,

DDMAC (HFD-42)

Lisa Stockbridge, Ph.D., Regulatory Review Officer DMAC (HFD-42)

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)

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

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

External Attendees:

Ross Lobell, Senior Manager, Worldwide, Regulatory Affairs

Bill Merinc, Senior V.P., Worldwide Regulatory Affairs

Byron Scott, V.P., FDA Liaison Group Worldwide Regulatory Affairs

Stuart Kolinsky, J.D., Assistant General Counsel, Warner Lambert

Randall Whitcomb, M.D., V.P., Drug Development

Fred Hershenson, Ph.D., V.P. Drug Development

Meeting Objectives:

To discuss proposals from sponsor regarding the use of the tradename change from "femHRT" to "femhrt".

Background:

The sponsor was informed via teleconference September 29, 1999, of the decision by FDA that the proposed tradename **femHRT** was not approved. During a teleconference October 4, 1999, FDA proposed the tradename "**femhrt**". The sponsor requested a follow-up teleconference to further discuss proposals offered by FDA regarding the new tradename and to discuss timelines on the use of the name in the label.

Discussion:

Sponsor Comments

- the sponsor proposes that all promotional materials have lower case "**femhrt**" with a launch date in January
- to maintain consistency it is requested that all other material, the foil packaging, carton and labeling maintain the previous tradename and logo "**femHRT**" for the first 3 months
- promotional materials include printed material; no audio ads or TV ads have been planned
- it is possible that by using the old tradename "**fem-HRT**" for the first 3 months then switching to the new tradename **femhrt** (pronounced fem'-ert) that the two logos would be on the shelf at the same time; time period for overlap cannot be estimated
- the change in the printing of the name is similar to the change that occurs when changing the logo colors for promotional and labeling materials
- changes in logos are common and should not create confusion for patients
- name and/or medication errors may be minimized by letters to the Pharmacist and Health Care Providers informing them of the change from **femHRT** to **femhrt**

FDA Comments

- there is a known risk the sponsor assumes in arranging printed materials prior to their approval
- FDA proposes that the sponsor change all promotional material, carton and labeling to reflect the new tradename "**femhrt**"
- primary packaging, (foil blisters and foil pouches) may remain with the old tradename "**femHRT**" until the next production
- there is the potential for increased confusion to the pharmacist and patients if both tradename logos are on the shelf at the pharmacy at the same time; FDA hopes to minimize this confusion by having all outer packaging read "**femhrt**"
- letters to the pharmacist and health care providers could clarify the differences in the tradename found on the primary and secondary packaging in case patients raise a concern

- marketing staff should be informed as to the correct pronunciation of the name, "fem'-ert" or the like, but not "fem-H-R-T" or "fem-heart"
- all letters of the new logo should be in the same font and color, not giving any emphasis to any one part of the name

Decisions Reached:

1. Sponsor agrees to "femhrt" as the new tradename for their product.
2. Sponsor agrees to pronunciation of the new tradename "fem'-ert".
3. Sponsor agrees to the terms of the use of the name in upcoming promotional materials, carton packaging and labeling.
4. Primary packaging (foil blisters and pouches) will use the old tradename "femHRT" until the next production.

Action Items:

1. Sponsor will make submission to NDA confirming agreement for change in tradename, and labeling prior to approval.

(Agreement submission from sponsor received October 12, 1999, dated October 8, 1999.)

2. Changes to the patient package insert and physician package insert will be reflected in the draft label submission to the NDA.

(Draft labeling with revised trademark received October 13, 1999; dated October 12, 1999.)

/S/
Minutes Preparer: 10/29/99

/S/
Meeting Chair

single

MEETING MINUTES

Date: October 4, 1999

Time: 10:30-12:00 p.m.

Location: Parklawn; 17B43

NDA: 21-065

Drug: Fem HRT (Norethindrone acetate and ethinyl estradiol)

Indication: HRT (treatment of vasomotor symptoms, and osteoporosis)

Type of meeting: Status and labeling (internal)

FDA lead: Dr Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

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

Joanna Zawadzki, M.D. Medical Officer, Division of Metabolic and Endocrine Drug Products, DMEDP, (HFD-510)

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

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

Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)

Venkat Jarugula, Ph.D., Pharmacokinetics Reviewer, DRUDP (HFD 580)

Lisa Stockbridge, Ph.D., Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC (HFD-42)

Karen Lechter, Ph.D., J.D., Social Science Analyst, DDMAC, (HFD-42)

Molly Fischer, MPH, CRNP, Regulatory Review Officer, DDMAC (HFD-42)

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

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

Meeting Objectives

1. To report on status of reviews and discuss issues related to approvability of NDA
2. To review draft label

Background:

Label received from sponsor September 27, 1999, dated September 10, 1999, and circulated to reviewers; internal meeting scheduled to include reviewers from DDMAC, and DMEDP.

Discussion

Chemistry

- Labeling Nomenclature Committee has found two drugs that are look-a-likes to FemHrt and did not approve the proposed name
- stability data did not support the proposed month shelf life, FDA proposed month shelf life and it was agreed that an 18-month shelf life will be acceptable
- the sponsor has agreed to tighten specifications
- establishment inspections have been completed

Biopharm

- briefing with biopharm is scheduled for October 12, 1999; final review will follow the briefing

DMEDP

- review is pending
- recommending approval of 1/5 dose only

Label was reviewed

(see attached comments from Dr. Mann regarding recommendations for labeling changes dated October 6, 1999)

Decisions Reached:

- Osteoporosis indication will be included in the label
- there will be one action letter sign-off with two signature blocks
- DRUDP will draft the approval letter

Action Item:

- labeling comments to be conveyed to sponsor within 2 days
comments sent to sponsor via fax
October 6, 1999
- Sponsor will be asked to make labeling changes after teleconference October 8, 1999.
- DDMAC will finalize review of patient package insert for review by DRUDP prior to teleconference October 8, 1999.
consult received October 7, 1999, and distributed to reviewers
- comment to be conveyed to sponsor:
in vitro dissolution specifications for both NA and EE should be revised to Q= [] at [] minutes
completed October 6, 1999, via telephone followed by fax

/S/

Minutes Preparer

/S/

Chair Concurrence

10/29/99

Attachment #1 Labeling comments for Physician Package Insert from DRUDP for
NDA 21-065

Teleconference Minutes

OCT 29 1999

Date: October 1, 1999

Time: 12:30-12:45 p.m.

Location: Parklawn: Rm. 17B-43

NDA: 21-065

Drug: femhrt (Norethindrone acetate and ethinyl estradiol)

Indication: Relief of vasomotor symptoms

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: Chemistry Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D.

External Lead: Sean Brennan

Meeting Recorder: Dornette Spell-LeSane.

FDA Attendees:

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

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @DRUDP

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

External Attendees:

Ross Lobell, Manager, FDA Liaison

Sean Brennan, CMC regulatory affairs

Leonard Lecosky, Chemist

Meeting Objective:

To discuss response to chemistry deficiencies submitted by the sponsor.

Background:

Sponsor responded to chemistry deficiencies via submission dated September 29, 1999; FDA requested a teleconference to discuss responses to chemistry deficiencies and to further request information.

Discussion:

FDA finds the following proposals from the sponsor acceptable:

1. Northindrone acetate specification will be set to meet [redacted] release limits.

2. As a Phase 4 commitment, [redacted]

- [REDACTED]
3. The 18-month expiration dating for the drug product is acceptable. full term data on three batches of each strength and package must be submitted as a prior approval supplement in order for extension of expiration dating to be considered

Action Items:

- Sponsor to submit to the NDA the above agreements in writing
Fax copy of submission received October 1, 1999; hard copy received October 4, 1999.
- Meeting minutes to be exchanged with sponsor within 30 days

/S/

Minutes Preparer

/S/

10/29/99
Concurrence, Chair

cc:

Original NDA 21-065

HFD-580/DivFile

HFD-580/Spell-LeSane

HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth/Hoberman/

drafted: dsl, 10/14/99

concurrence: Ortwerth, 10.28.99, Rhee, 10.28.99,
final:

TELECONFERENCE MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

OCT 13 1999

Teleconference Minutes

Date: September 30, 1999 Time: 11:55-12:10 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: Information Request

Meeting Chair: Dan Davis, M.D.

External Lead: Ross Lobell

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Dan Davis, MD, Medical Officer, Division of Reproductive and Urologic Drug Products.
DRUDP, (HFD-580)

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

External Attendees:

Ross Lobell, Sr. Manager, Worldwide Regulatory Affairs

Meeting Objective:

To convey clinical review comments.

Background:

NDA currently under review with a user fee goal date of October 17, 1999. Teleconference was requested by FDA to convey clinical comments and request information needed to complete review.

Discussion:

1. What were the main issues surrounding the delayed submissions for this NDA?
2. Have there been any applications to "other regulatory agencies", as stated in your summary, and if so, when?
3. What were the specific reasons for the eleven patients with "Other/Administrative" early withdrawal in Study 390?

4. Regarding the incidences of Thromboembolic events:

- Exactly where (volume and page #) are more detailed information about the six women with thromboembolic adverse events? (Table 28, page 41 of 63 of the ISS. refers to incorrect references and the statements are brief).
- Is there any additional information for the six women with thromboembolic AE's? Specifically regarding:
 - obesity
 - history of thromboembolic events
 - CHF
 - lower extremity trauma (fx, injury, surgery)
 - prior OC use
- Were there any placebo cases of thromboembolic events?
- Were there any "estrogen only" cases of thromboembolic events?

5. From the revised physician label submitted by the sponsor dated September 10, 1999, received September 27, 1999:

- p. 10 of 27 figure 2, "mean hotflash frequency"
 - The small box indicates number of patients randomized to be 66, 65, 64. actual numbers according to review were 67, 67, and 65. Please explain.
- p. 12 "Irregular Bleeding/Spotting"
 - Please define cumulative amenorrhea and how the rate 87-72% was determined
 - From the 12-month graph, please clarify the 40-50% at three months and how this differs from the 12-week statement.

Action Items:

- Comments e-mailed to sponsor: September 30, 1999.
- Sponsor to submit response by COB October 1, 1999.
- Final minutes to be exchanged with sponsor within 30 days.

Note:

Sponsor's response to clinical request for information was received October 4, 1999 via e-mail. The Sponsor will follow-up with a hard copy submission to the NDA October 5, 1999.

/S/

Minutes Preparer

10/15/99
/S/

Concurrence, Chair

OCT 15 1999

Teleconference Minutes

Date: September 29, 1999 **Time:** 1:10-1:45 p.m. **Location:** Parklawn; Rm. 17B-43

NDA: 21-065 **Drug:** Fem HRT (norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: Guidance

Meeting Chair: Lisa Rarick, 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)

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP

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

External Attendees:

Ross Lobell, Manager, FDA Liaison

Mary Taylor, Regulatory Affairs

Sean Brennan, CMC Regulatory Affairs

Randall Whitcomb, M.D., Drug Development

Meeting Objective:

1. To convey recommendations from the Labeling and Nomenclature Committee regarding proposed drug name.
2. To convey initial clinical review comments regarding the highest proposed dose.

Background:

The Labeling and Nomenclature Committee (LNC) approved FEM HRT October 1, 1996 during the IND process. LNC was asked to review again the name for this NDA review cycle. The Division was notified by the LNC September 28, 1999, of the unacceptability of the name FemHRT.

Discussion:

Item#1

FDA Comments

- The following three reasons regarding the unacceptability of the name FemHRT were provided to the sponsor:
 1. There were two names the LNC found to be too close to the name FemHRT; they were FemStat and [redacted]
 2. The name might be misinterpreted to indicate a relationship of the drug to the heart, since HRT is a common abbreviation for heart.
 3. HRT implies "Hormone Replacement Therapy" which may give an unfair advantage to this product, one of many.
- ODE II raised significant concerns regarding the proposed name and concurs with the LNC.
- The sponsor may proceed with the dispute process to appeal this decision.
- Absence of a tradename will not delay a Division action for this NDA.

Sponsor:

- there was no intention to pursue a cardiovascular indication in the label
- there was no intention for the name to imply use for the heart
- this product name is congruent with other Parke-Davis products, such as FemPatch
- the target audience are OB/GYN physicians and disagree that HRT is commonly abbreviated for the heart among the group of physicians

Item#2

FDA Comments:

On clinical review of the application, there appears to be [redacted]
[redacted] for the following reasons:

Sponsor:

[Redacted]

Action Items:

- Sponsor to submit [Redacted] for the [Redacted]
- Sponsor should consult with DMEDP regarding the [Redacted]
- DRUDP to schedule a teleconference to convey clinical request for information.
(Scheduled for September 30, 1999)

[Redacted] /S/

Minutes Preparer

[Redacted] /S/ 4/15/99

Concurrence, Chair

cc:
Original NDA 21-065
HFD-580/DivFile
HFD-580/Spell-LeSane
HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth/Hoberman/

drafted: dsl, 9/29/99 NDA 21-065
concurrence: Ortwerth, 10.1.99 Rarick, 10.4.99, Mann, 10.4.99, Rumble, 10.4.99
final: Spell-LeSane, 10.11.99

TELECONFERENCE MINUTES

OCT 13 1999

Teleconference Minutes

Date: September 28, 1999 Time: 1:36-1:45 p.m. Location: Parklawn; 18B09

NDA: 21-065 Drug: FemHRT (Norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: CMC Labeling

Meeting Chair: Michael Ortwerth, Ph.D.

External Lead: Sean Brennan, Ph.D.

Meeting Recorder: Michael Ortwerth, Ph.D.

FDA Attendees:

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP

External Attendees:

Sean Brennan, Ph.D., CMC Regulatory Affairs

Meeting Objective:

To obtain clarification on the omission of [redacted] from the HOW SUPPLIED section of labeling.

Background:

The sponsor submitted a labeling update, "Update as of September 10, 1999," that included changes to the HOW SUPPLIED section of patient and physician inserts.

Discussion:

Chemistry: *The HOW SUPPLIED section of the most recent labeling update no longer lists the [redacted] container/closure system for the drug product. Could you please clarify why this information was omitted from the most recent labeling update.*

Sponsor: The [redacted] is for physician samples only. Typically, these are not included in the labeling and, therefore, were removed.

Decision Reached:

The sponsor's reply is acceptable.

Action Items: NA

/S/ 13-SEP-1999
Minutes Preparer/ Chair Concurrence

CC: Original
HFD/Div Files
HFD-580/Spell-Lesane
HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Ortwerth/Jordan/Parekh/
Kammerman/Hoberman/

Concurrence:
Draft: Ortwerth 30-SEP-1999
Final: Colangelo for Rumble, 10.08.99

APPEARS THIS WAY
ON ORIGINAL

OCT 14 1999

Teleconference Minutes

Date: September 27, 1999 **Time:** 2:30-3:10 p.m. **Location:** Parklawn; Rm. 17B-43

NDA: 21-065 **Drug:** Fem-HRT (northindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: Chemistry Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D.

External Lead: Sean Brennan

Meeting Recorder: Diane Moore

FDA Attendees:

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

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP

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

External Attendees:

Ross Lobell, Manager, FDA Liaison

James Symons, M.D., Clinical

Sean Brennan, CMC regulatory affairs

Leonard Lescosky, Chemist

Meeting Objective:

To discuss chemistry deficiencies noted in review of this NDA.

Background:

Sponsor responded to chemistry deficiencies via submission dated July 20, 1999. FDA requested a teleconference to discuss responses to chemistry deficiencies and to request further information.

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ON ORIGINAL

Discussion:**FDA Comments:**

1. The revised Uniformity of Dosage Units Specifications was deemed adequate.
2. To assure no loss of potency from acceptance of the drug substance to the start of the drug product manufacturing, please establish and perform acceptance testing for the drug substance norethindrone acetate in accordance with the drug substance supplier's certificate of analysis specifications.

4. The [] and specification for tablet release is acceptable. [] specification for release of the tablet should be established.
5. To accept the specifications for EE-related impurities for the [] FemHRT dose, please include further adoption of OPTION 1 below to your drug product specifications (i.e., inclusion of an EE Assay at Release test specification of [] Label Claim). Another possibility is presented as OPTION 2. If the [] is withdrawn from the NDA then the specifications proposed is acceptable.

Drug Product Test for 0.5/2.5 dose.	Sponsor's Proposed Specifications	Reviewer's Proposed Specifications: OPTION 1	Reviewer's Proposed Specifications: OPTION 2
EE Assay (Release)			
EE Related Impurities			
[]			
[]			
Other individual Degradation Products/Impurities			
Total Degradation Products/Impurities			

6. Please submit to the NDA a statement that extension of expiration will be based on real-time data from the first three post-approval commercial product batches.
7. The data and analyses provided to the NDA in support of expiration dating of [] months is not acceptable. Therefore, an expiry of [] months is granted for the commercial drug product.
8. Commercial batches should be used for extension of stability.

Sponsor Comments:

1. Sponsor is requesting USP specifications be applied for both ethinyl estradiol and northindrone acetate (acceptance testing is tighter for northindrone acetate with the drug substance supplier than with USP).

Action Items:

- Sponsor should submit a revised post approval stability commitment. Submit statement that extension will be based on real-time data from first three post-approval commercial product batches.
- Sponsor to submit full responses to requests described above within 2 days.
(Fax received September 29, 1999)
- Meeting minutes to be exchanged with sponsor within 30 days.

/S/

Minutes Preparer

/S/ 10/14/99

Concurrence, Chair

cc:

Original NDA 21-065

HFD-580/DivFile

HFD-580/Spell-LeSane

HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth/Hoberman/

drafted: dsl, 9/30/99 NDA 21,065

concurrence: Rumble, 10.4.99/Ortwerth, 10.1.99, Rhee, 10.12.99

final: Spell-LeSane, 10.13.99.

TELECONFERENCE MINUTES

OCT 12 1999

Teleconference Minutes

Date: September 17, 1999 **Time:** 9:00-10:30 a.m. **Location:** Parklawn; Rm. 17B-43

NDA: 21-065 **Drug:** Fem HRT (Norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: Labeling

Meeting Chair: Marianne Mann, M.D.

External Lead: Ross Lobell

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP HFD-580)

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

Lisa Stockbridge, Ph.D., Regulatory Review Officer, Division of New Drug Marketing and Advertising (DDMAC)

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP

Venketeswar Jarugular, Ph.D., Pharmacokinetics Reviewer, DPEII @ DRUDP (HFD 580)

Joan Zawadzki, Medical Officer, Division of Metabolics and Endocrine Drug Products, (DMEDP; HFD-510)

David Hoberman, Statistician, DB II @ DRUDP

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

External Attendees:

Ross Lobell, Manager, FDA Liaison

Mary O'Sullivan, Regulatory Affairs

Mary Taylor, Regulatory Affairs

James Symons, Clinical Group

Rochelle Hannley, Clinical Group

Rebecca Boyd, Pharmacokinetics

Elizabeth Attias, Marketing

Andrew Panagy, Marketing

Len Lescosky, Regulatory Chemistry

Meeting Objective:

To continue labeling discussions started September 10, 1999, regarding draft labeling submitted with comments by the sponsor August 27, 1999.

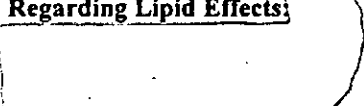
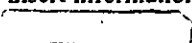

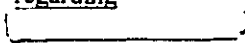
Background:

The Division received labeling comments from the Sponsor September 9, 1999. A labeling meeting was held September 10, 1999. This teleconference was scheduled to continue the discussions regarding the draft label.

Discussion:

Labeling changes continued using the outline below; discussions began with page 17, Indications and Usage):

CHANGE	REASON	FDA response
It is desired to retain the order of active ingredient presentation as NA/EE	This order of presentation provides continuity between our other NA/EE containing products.	OK
Accordingly, the enclosed package insert has been modified to reflect this fact		
Page 6: Clinical Pharmacology: We have retained the last sentence at the end of paragraph 1	The inclusion of this statement informs the reader that there is no documented evidence of activity differences between ethinyl estradiol and endogenous estrogens.	f/u from September 10, 1999 meeting: <i>DDMAC finds this statement to be true and will allow in the label</i>
Page 6: Clinical Pharmacology: A paragraph regarding progestin compounds has been added	This provides important background information on progestins to balance the estrogen information given	OK
Page 7: Clinical Pharmacology: Last paragraph of the section has been replaced with "continuous administration"	Due to the nature of this product, the use of the word "continuous" is more appropriate since continuous exposure to progestin occurs.	OK
Page 7: Pharmacokinetics: Sentence from Geriatrics section moved to just above figure 1.	We concur with the Agency that this sentence is inappropriate for the Geriatrics section, however, it does provide important information and so has been relocated.	will review
Page 9: Table 1: information not included	The most important information for chronic use is the Day 87, steady state information.	please re-evaluate table
Page 10: Race: 		Studies include 90% Caucasian women, which is not acceptable for a race claim.
Page 14: Endometrial Hyperplasia: 12 and 24 month data are reflected in the table 3.	This is the most useful data to the reader	changes recommended
Page 15: Table 4: Cumulative Amenorrhea: The 12 week data	Due to the method of collection of this data for the study, 12-month amenorrhea data can not	Sponsor may submit additional data. FDA requests that

were retained.	be clearly presented in the package insert. However, we have just completed an interim analysis on bleeding/spotting data from the 376-401 study (original IND protocol submission date February 6, 1998; serial 190) which can provide comparative data over 6 months. This information is not part of the NDA and we would like to discuss the possibility of including this information in the package insert, providing there would be no impact on the review clock. See text below for an additional description of this data.	available data be shown given 12 month data which is not yet available.
Page 17: Information Regarding Lipid Effects; 	This provides useful information to put FemHRT effects on lipids into perspective.	Clinical relevance for ratios are misleading. Please delete all ratio data from the chart
Page 17: Following Table 4: insert information regarding 	 information was collected for FemHRT and due to its increasing importance, should be reflected in the label.	DDMAC request information regarding  found in the NDA submission. DDMAC will review and make recommendations after review of information.

APPEARS THIS WAY
ON ORIGINAL

	<u>Beginning of labeling discussion</u> <u>continued from September 10, 1999</u>	
<p>Page 17: Indications and Usage: [redacted]</p> <p>Addition of indication for protection of the endometrium</p> <p>APPEARS THIS WAY ON ORIGINAL</p>	<p>Agreement was reached during the June 3, 1996 pre NDA meeting that the available studies for FemHRT to be included in the NDA submission would: [redacted] indication in the labeling. The Agency's February 4, 1997 response to Parke-Davis meeting minutes did not contest this agreement. In addition, cytology data were collected in the 376-343 study. A summary of this data is presented below.</p> <p>The Indication for endometrial protection is justified on the basis of studies conducted as described in "GUIDANCE FOR THE CLINICAL EVALUATION OF COMBINATION ESTROGEN/PROGESTIN-CONTAINING DRUG PRODUCTS USED FOR HORMONE REPLACEMENT THERAPY OF POSTMENOPAUSAL WOMEN"</p> <p>APPEARS THIS WAY ON ORIGINAL</p>	<p>There is not enough data to support the indication of [redacted] With the new guidance, indications will need to be supported by studies. All current applications are asked to follow these guidelines. After the guidance has been made final, all sponsors will be asked to comply.</p> <p>Subset of patients may be allowed using clinical and vaginal maturation data, and for duration of treatment to show efficacy approx. 3-6 months may be acceptable, sponsor would have to propose and this would be a review issue.</p> <p>Protection of the endometrium is not an indication but a safety benefit and should be described in the clinical trial section.</p>
<p>Page 20: Endometrial Cancer: Second paragraph. Original last sentence referring to hazards of synthetic vs. natural estrogens at equivalent doses was retained.</p>	<p>This information is necessary to let the reader know that synthetic and natural estrogens behave similarly in order to avoid confusion between the two.</p>	<p>OK</p>
<p>Page 20: Breast Cancer: Last sentence of last paragraph referring to NCI/SEER database retained</p>	<p>This information provides perspective on FemHRT results relative to an established, well-respected database commonly used by Industry, Academia and FDA.</p>	<p>Comparison using NCI data is unequivocal data. The division would like the [redacted] data removed</p>
<p>Page 23: 2. Use in Hysterectomized Women: Delete last sentence of this section.</p>	<p>This information is not necessarily relevant to hysterectomized women. Is there a reference which would justify this sentence here?</p>	<p>OK</p>
<p>Page 23: 6: [redacted] This section was deleted</p>	<p>Use in patients with [redacted] is already contraindicated</p>	<p>Please move information on [redacted] disease to the precautions section of the label</p>
<p>Page 26: 5: [redacted] This section was deleted</p>	<p>We know of no literature that would support this. Is there a reference for this statement?</p>	<p>Diabetic patients should be observed while taking progestin, Impaired glucose tolerance should remain in the Precaution section</p>

<p>Page 30 and 31: How Supplied: This section was updated to remove the [redacted] and to remove the [redacted]</p>	<p>The [redacted] are intended to be physician samples and will not be sold commercially.</p>	<p>resolved by Chemistry</p>
<p>Page 31: Storage Statement: We plan to change the storage statement on the package insert, but wish to retain the original wording on the remainder of product labeling until initial packaging components are exhausted.</p>	<p>Long lead times for packaging materials have forced us to order them prior to the receipt of your comments. We will revise the storage statement on the remaining labeling with the first re-order of materials.</p>	<p>resolved by Chemistry</p>

APPEARS THIS WAY
ON ORIGINAL

Action Items:

- Sponsor to submit draft labeling incorporating FDA comments for review by September 27, 1999.

(Label submitted September 27, 1999 through secure E-mail arranged by the sponsor)

- Project Manager to schedule internal meeting to discuss draft labeling.

(Internal meeting scheduled for October 4, 1999)

- Project Manager to schedule teleconference for review of draft labeling to be submitted by the sponsor.

(T-con with sponsor scheduled for October 5, 1999)

- Submission sent by the sponsor dated September 16, 1999 will be shared with reviewers after teleconference today.

/S/
Minutes Preparer

/S/
Concurrence, Chair
10/12/99

cc:

Original NDA 21-065

HFD-580/DivFile

HFD-580/Spell-LeSane

HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth/Hoberman/

HFD-42/Stockbridge

drafted: dsl, 9/28/99 NDA 21,065

concurrence: Ortwerth, 10.1.99, Mann, 10.4.99, Zawadzki, 10.4.99 Rumble, 10.7.99,

final: Spell-LeSane, 10.11.99

TELECONFERENCE MINUTES

Electronic Mail Message

Date: 9/16/99 4:52:37 PM
From: Taylor, Mary (Mary.Taylor@wl.com)
To: 'SPELLLESANED@cder.fda.gov' ('SPELLLESANED@A1')
Subject: FemHrt Labeling Information

<<FemHRTlabeling0915.doc>>

Dornette,

Attached are the updated graphs and tables discussed last Friday as well as the location of the requested information. If you have any questions please give me a call. Ross is in DC.

Mary E. Taylor, MPH

Sr. Director

Worldwide Regulatory Affairs

Parke-Davis Pharmaceutical Research Division

734/622-5000 Fax 734/622-3283

APPEARS THIS WAY
ON ORIGINAL

9/15/99

Dornette,

We found the meeting this past Friday to be most useful and are looking forward to an equally productive meeting this Friday.

Below is the additional information requested from Parke-Davis during the meeting:

With regard to Page 9, Table 1: A revised table to include relevant Day 1 pharmacokinetic parameters is given below:

TABLE 1. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters^a Following Administration of FemHRT 1/10 Tablets

	C _{max}	t _{max}	AUC(0-24)	CL/F	t _{1/2}
Norethindrone	ng/mL	hr	ng · hr/mL	mL/min	hr
Day 1	6.0 (3.3)	1.8 (0.8)	29.7 (16.5)	588 (416)	10.3
(3.7)					
Day 87	10.7 (3.6)	1.8 (0.8)	81.8 (36.7)	226 (139)	13.3
(4.5)					
Ethinyl Estradiol	pg/mL	hr	pg · hr/mL	mL/min	hr
Day 1	33.5 (13.7)	2.2 (1.0)	339 (113)	ND ^b	ND ^b
Day 87	38.3 (11.9)	1.8 (0.7)	471 (132)	383 (119)	23.9
(7.1)					

^a C_{max} = Maximum plasma concentration; t_{max} = time of C_{max}; AUC(0-24) = Area under the plasma concentration-time curve over the dosing interval; and CL/F = Apparent oral clearance; t_{1/2} = Elimination half-life; ^bND=Not determined

**APPEARS THIS WAY
ON ORIGINAL**

1 Page(s) Redacted

Draft

Labeling

With regard to Page 15 Cumulative Amenorrhea:

We propose that both the 3 month graph and the 12 month graph be presented in the package insert. The 3 month data are more accurate and the 12 month data satisfy your need for long term information.

- **We understand your need for consistency in labeling between products, however, in reviewing the PremPro label 2 graphs are presented illustrating amenorrhea for all patients and for those completing 13 cycles. These data were collected using daily diaries. The Activelle labeling contains a graph of percentage of women bleeding each month out to 12 months. No cumulative data are presented. These data were also collected from daily diaries. Although the study duration is only 12 weeks, bleeding and spotting data in Study 376-390 (hot flash frequency and severity study) were collected on daily diaries. We can provide the cumulative graph (as in PremPro) or the Percentage of Women with Bleeding graph (as in Activelle) in the label. The CHART data were collected by recall. Providing this data would be inconsistent with the other product labels.**
- **Recall data are unreliable and subject to bias. Bleeding and/or spotting data from the CHART Study were collected asking the patients to recall at each clinic visit whether they recalled any occurrence of bleeding and/or spotting since the previous clinic. In this study the minimum time between visits in the first year of this 2-year study was 1 month (study randomization to end of 1 month of treatment). Maximally the time interval between visits was 3 months (end of 3 months of treatment to end of end of 6 months of treatment; 6 months to 9 months of treatment and 9 to 12 months of treatment. The implication of relying on recall of events has been extensively evaluated in numerous studies and**

in a variety of therapeutic areas. For example, estimates of medical utilization was examined comparing both diary and health care provider interview and it was found that prevalence estimates were higher in the interview and that the interview were prone to recall bias (Bruijnzeels, et al 1998). Likewise, a study of rhinitis symptoms indicates recall bias related to recency of symptoms (Steward, et al 1997) which was also reflected in discrepancies between patient recall and medical records on the diagnosis and clinical assessment of spondyloarthropathy (Boyer, et al 1995). Finally, a study of the effect of recall on nonfatal injury rates for children and adolescents concludes that varying recall periods can have significant effects on the rate of events (Harel, et al 1994).

The above is not an inclusive summary of the effect of recall bias, but is intended to illustrate the breadth of effect across various diseases or health outcomes. The concern with regard to the FemHRT label discussion regarding bleeding and/or spotting data from CHART study is that it may be subject to the same bias and does not accurately reflect information collected in subsequent studies using daily reporting of events. This is illustrated in the cumulative amenorrhea data from CHART and 376-390.

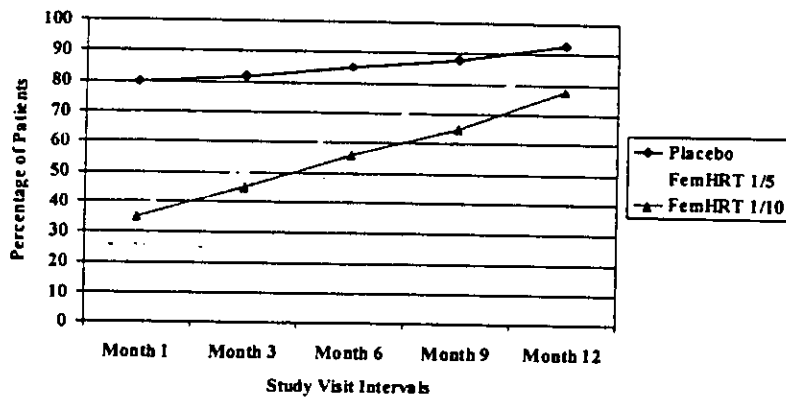
- Bleeding and spotting is one of the primary reasons women discontinue hormone replacement therapy. Prescription data indicate that this occurs within the first 6 months of therapy. While 12 month data would be useful to the physician, the 12 week data from the 376-390 study would also provide valuable information to the patient to make decisions regarding therapy*

In addition, we propose to replace the enclosed chart with the 12 month amenorrhea data acquired during study 376-401. A NDA supplement would be submitted post approval at the time the study report was available for submission to the Agency.

APPEARS THIS WAY
ON ORIGINAL

Proposed Cumulative Amenorrhea Chart:

Cumulative Amenorrhea from FemHRT™
CHART Study; ITT-LOCF



With regard to Page 17, Indications and Usage: The location of the
cytology information to support the

indication are located in RR720-03134 (protocol number 376-343). This information can be found in NDA volume 72 on NDA page 37(in square) or report page 1236, Appendix E.17.

With regard to Page 17, Quality of Life: Information regarding quality of life data collected during the clinical investigation of FemHRT can be found in RR 720-03946 (protocol 376-390). The report is located in NDA volume 101 which provides a narrative of the results (report page 41, NDA volume page 42). Appendix F.4 in NDA volume 107, beginning on NDA volume page 1 contains the data listings for quality of life. The reference for the instrument used is: Hilditch, JR., et.al. "A Menopause-Specific Quality of Life Questionnaire: Development and Psychometric Properties". Maturitas, 1996; 24:161-175. A copy of this reference will be supplied separately.

APPEARS THIS WAY
ON ORIGINAL

OCT 12 1999

Teleconference Minutes

Date: September 10, 1999 **Time:** 2:00-3:30p.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: Labeling

Meeting Chair: Marianne Mann, M.D.

External Lead: Ross Lobell

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)

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

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

Michael Ortwerth, Ph.D., Chemist, Division of New Drug Chemistry II @DRUDP

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

Joan Zawadzki, Medical Officer, Division of Metabolics and Endocrine Drug Products (DMEDP; HFD-510)

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

Dornette Spell-LeSane, NP-C, 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

Laskowski, Regulatory Chemistry

Meeting Objective:

1. To discuss labeling changes recommended by FDA
 2. To convey, for the record, FDA CMC comments previously conveyed to sponsor (via t-con August 31 and September 9, 1999 between chemistry representative and FDA chemistry reviewer) in response to IR letter sent August 27, 1999.
-

Background:

Draft Labeling changes from FDA were communicated to the Sponsor August 27, 1999. The sponsor accepted an invitation for a teleconference to discuss labeling changes. The Division received comments from sponsor September 9, 1999 for today's meeting. This NDA action date is October 17, 1999.

Discussion:

Chemistry:

August 31, 1999

IRQ8: Please provide sampling procedures for the drug product.

Sponsor Does the sampling procedures refer to the bulk drug product?

Chemistry: Yes, sampling procedures referred to in IR question number 8 do refer to the bulk drug product.

IRQ9: Please revise the specifications for the drug product as follows:

For Norethindrone acetate (NA): Please identify and qualify all unknown impurity peaks that appear at values of for the 1 mg NA tablets.

Sponsor: The ICH guidelines that the sponsor is aware of do not adhere to the requirements imposed by this question. What reference can be given to support this question?

Chemistry: The sponsor was informed that this issue would be further researched and clarified at a later date.

IRQ10: The Specifications and Test Methods for the Drug Product (Appendix 8; NDA Vol. 1.17) and the Methods Validation Package (Appendix 1-7; NDA Vol. 1.21) are not properly edited and this creates confusion in review. Please resubmit these sections of the NDA in triplicate with corrections.

Sponsor: What portions of the referenced sections are lacking clarity and what specific corrections are requested?

Chemistry: The sponsor was informed in more specific detail of the editing errors in these sections of the NDA application.

IRQ11: The Storage Statement for the drug product in Physician and Patient Package Inserts should be corrected and should read "Store at 25°C (77°F): Excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]"

Sponsor: What guidance document supports the request for this specific storage statement.

Chemistry: The sponsor was informed that the answer to this question would be determined and relayed to the sponsor at a later date.

Additional Chemistry Comments:

Concerning the issue of reprinting of labeling to include the requested labeling statement for storage temperature found in IR question number 11,

The sponsor does not need to make changes at this time to the statement of storage temperature on the Drug Product Packaging.

1. It is requested that the statement be changed in Drug Product Physician and Patient Labeling at this time, so as to avoid the submission of a future labeling supplement.
2. In addition, it is requested that the sponsor commit to including the requested storage temperature statement outlined in IR question number 11 in the next printing of Drug Product Packaging. This is acceptable since the current statement is more stringent than the requested statement.

The current storage temperature statement on Drug Product Packaging is...

"Store at controlled room temperature [See USP]."

Note: See attached additional Chemistry t-comments from September 9, 1999

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ON ORIGINAL**

Labeling Discussions:

- Labeling changes outlined below were discussed. The sponsor outlined the changes recommended by FDA and their response if agreed and rationale if they did not agree.

CHANGE	REASON	FDA response
It is desired to retain the order of active ingredient presentation as NA/EE	This order of presentation provides continuity between our other NA/EE containing products.	OK
The [redacted] Accordingly, the enclosed package insert has been modified to reflect this fact	[redacted]	sponsor may [redacted] and seek approval as a supplement at a later date
Page 6: Clinical Pharmacology: We have retained the last sentence at the end of paragraph 1	The inclusion of this statement informs the reader that there is no documented evidence of activity differences between ethinyl estradiol and endogenous estrogens.	DDMAC will follow up (see label meeting 9/17/99)
Page 6: Clinical Pharmacology: A paragraph regarding progestin compounds has been added	This provides important background information on progestins to balance the estrogen information given	OK
Page 7: Clinical Pharmacology: Last paragraph of the section [redacted] has been replaced with "continuous administration"	Due to the nature of this product, the use of the word "continuous" is more appropriate since continuous exposure to progestin occurs.	OK
Page 7: Pharmacokinetics: Sentence from Geriatrics section moved to just above figure 1.	We concur with the Agency that this sentence is inappropriate for the Geriatrics section, however, it does provide important information and so has been relocated.	will review
Page 9: Table 1 [redacted] information not included	[redacted] The most important information for chronic use is the Day 87, steady state information.	please re-evaluate table
Page 10: Race: [redacted]	Sufficient numbers of non-Caucasian patients were enrolled to allow detection of large differences in pharmacokinetics, if present.	studies include 90% Caucasian women, which is not acceptable for a race claim.
Page 14: Endometrial Hyperplasia: 12 and 24 month data are reflected in the table 3.	This is the most useful data to the reader	changes recommended
Page 15: Table 4: Cumulative Amenorrhea: The 12 week data were retained.	Due to the method of collection of this data for the [redacted] study, 12 month amenorrhea data can not be clearly presented in the package insert. However, we have just completed an interim analysis on bleeding/spotting data from the 376-401 study (original IND protocol submission date February 6, 1998; serial 190) which can provide	Sponsor may submit additional data. FDA requests that available data be shown given 12 month data is not yet available.

	comparative data over 6 months. This information is not part of the NDA and we would like to discuss the possibility of including this information in the package insert, providing there would be no impact on the review clock. See text below for an additional description of this data.	
Page 17: Information Regarding Lipid Effects:	This provides useful information to put FemHRT effects on lipids into perspective.	clinical relevance for ratios are misleading. Please delete all ratio data from the chart.
Page 17: Following Table 4: insert information regarding	information was collected for FemHRT and due to its increasing importance, should be reflected in the label.	DDMAC request information regarding found in the NDA submission. DDMAC will review and make recommendations after review of information. end of labeling meeting to resume September 17, 1999
Page 17: Indications and Usage: Addition of indication for protection of the endometrium	Agreement was reached during the June 3, 1996 pre NDA meeting that the available studies for FemHRT to be included in the NDA submission would indicate in the labeling. The Agency's February 4, 1997 response to Parke-Davis meeting minutes did not contest this agreement. In addition, cytology data were collected in the 376-343 study. A summary of this data is presented below. The Indication for endometrial protection is justified on the basis of studies conducted as described in "GUIDANCE FOR THE CLINICAL EVALUATION OF COMBINATION ESTROGEN/PROGESTIN-CONTAINING DRUG PRODUCTS USED FOR HORMONE REPLACEMENT THERAPY OF POSTMENOPAUSAL WOMEN"	
Page 20: Endometrial Cancer: Second paragraph. Original last sentence referring to hazards of synthetic vs. natural estrogens at equivalent doses was retained.	This information is necessary to let the reader know that synthetic and natural estrogens behave similarly in order to avoid confusion between the two.	
Page 20: Breast Cancer: Last sentence of last paragraph referring to NCI/SEER database	This information provides perspective on FemHRT results relative to an established, well-respected database commonly used by Industry, Academia	

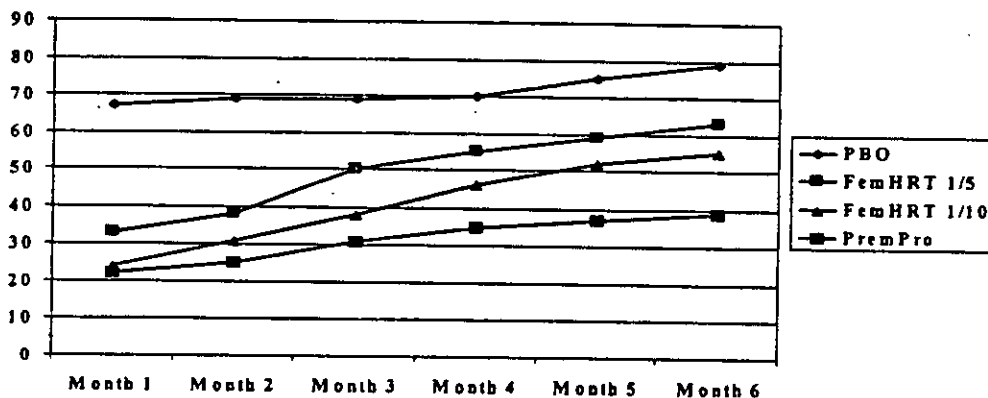
Page 30 and 31: How Supplied: This section was updated to remove the [redacted] and to remove the [redacted]	The [redacted] are intended to be physician samples and will not be sold commercially.	
Page 31: Storage Statement: We plan to change the storage statement on the package insert, but wish to retain the original wording on the remainder of product labeling until initial packaging components are exhausted.	Long lead times for packaging materials have forced us to order them prior to the receipt of your comments. We will revise the storage statement on the remaining labeling with the first re-order of materials.	

ADDITIONAL NARRATIVE REGARDING BLEEDING AND SPOTTING DATA FROM STUDY 376-401

In a double-blind, placebo-controlled, trial of FemHRT daily reports of bleeding or spotting were obtained. The study also included an unblinded treatment group of continuous combined conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) marketed as Prempro™. An analysis all patients from this ongoing study at the 6-month time for cumulative amenorrhea is summarized in Figure 1. There were statistically significantly more women amenorrheic who were administered FemHRT 1/5 compared to Prempro at every time point and at Months 5 and 6 for FemHRT 1/10.

Figure 1:

**Cumulative Amenorrhea from Early Analysis
for 376-401 Study - 6 Month Time Point -
ITT, LOCF**



* = $p < .05$ FemHRT compared to Prempro

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Decisions made:

- Sponsor to submit [redacted] data for review by DDMAC
- Sponsor to review FDA comments and continue working on patient package labeling

Action Items:

- DRUDP to schedule a teleconference to continue labeling discussions
Scheduled for September 17, 1999

Attachment:

Teleconference minutes from September 9, 1999 between Dr. Michael Ortwereth, Chemistry reviewer and Mr. Lescosky of Parke-Davis

[redacted] /S/
Minutes Preparer

1
[redacted] /S/
Concurrence Chair
10/12/99

cc:

Original NDA 21-065
HFD-580/DivFile
HFD-580/Spell-LeSane
HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth/Hoberman/
HFD-42/Stockbridge

drafted: dsl, 9/28/99 NDA 21,065

concurrence: Rumble, 9.30.99, Stockbridge, 9.30.99, Ortwerth, 10.01.99, Mann, 10.04.99,

final: Spell-LeSane, 10.11.99

TELECONFERENCE MINUTES

Mr. Lescosky then continued our conversation with his request for clarification of questions in the IR letter dated 27-AUG-99 sent to the sponsor concerning CMC issues.

IRQ2: *Please establish and perform acceptance testing for the drug substances norethindrone acetate and ethinyl estradiol in accordance with the drug substance supplier release specifications. All drug substance batches received by the drug product manufacturer, Duramed, outside of these specifications should not be accepted for manufacturing.*

SI2: Does this question imply a deficiency on the part of the drug substance supplier?

RR2: The sponsor was informed that I could not discuss deficiencies in relationship to a drug substance suppliers DMF. The sponsor was informed, however, that the question was based on the fact that no drug substance acceptance specifications or testing methods were supplied in the NDA for the drug product manufacturer Duramed.

SR2: The sponsor replied that Duramed's drug substance acceptance specifications for norethindrone acetate and ethinyl estradiol would be submitted in response to IR question number 2.

IRQ10: *The Specifications and Test Methods for the Drug Product (Appendix 8; NDA Vol. 1.17) and the Methods Validation Package (Appendix 1-7; NDA Vol. 1.21) are not properly edited and this creates confusion in review. Please resubmit these sections of the NDA in triplicate with corrections.*

SI10: The sponsor stated that editing errors found in the sections referred to in IR question number 10 had been corrected and that these sections of the NDA would be resubmitted to application. The sponsor also asked if there were any other errors found by this reviewer that would need further correction.

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RR10: The sponsor was informed that to the current knowledge of this reviewer no further corrections would be necessary at this time.

The sponsor was also asked for clarification of another detail in concerning their application.

Q: Is Parke-Davis the drug product distributor?

SR: Yes, Parke-Davis is the drug product distributor. Duramed, the drug product manufacturer, releases the drug product to Parke-Davis who warehouses the drug product for distribution.

APPEARS THIS WAY
ON ORIGINAL

OCT 12 1999

MEETING MINUTES

Date: September 8, 1999

Time: 9:00-10:00 a.m. Location: Parklawn; 17B-43

NDA: 21-065

Drug: Fem HRT (Norethindrone acetate and ethinyl estradiol)

Indication: HRT (treatment of vasomotor symptoms and osteoporosis)

Type of meeting: Labeling (internal)

FDA lead: Dr. Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

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

Venkat Jarugula, Ph.D., Pharmacokinetics Reviewer, DRUDP (HFD 580)

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

Meeting Objective

To review label and discuss comments to be conveyed to sponsor during t-con scheduled for September 10, 1999.

Background:

FDA comments to sponsors draft labeling were conveyed to the sponsor August 27, 1999, through secured e-mail system arranged by the sponsor. A teleconference was held August 31, 1999 in which urgent labeling comments were conveyed to the division. Additional comments were received from sponsor to discuss at internal labeling meeting.

Discussion

Label was reviewed

Sponsor comments:

1. The Sponsor would like to keep order of presentation of active drugs in label as "progestin/estrogen".

FDA response: Following internal discussion, the Division will allow the current order of active drug to stand as proposed by the sponsor.

2. The Sponsor would like to obtain advice on [redacted] from the current review in order to avoid the [redacted] being represented in the label until after current [redacted] are completed.

FDA response: The [redacted] this drug product is currently under review. Regulations require that if the [redacted] has been reviewed and approved then it must be included in the label. The sponsor may wish to withdraw the [redacted] before the action date and subsequently submit a supplement for the [redacted]

3. The sponsor believes that adequate data has been provided that supports race information and would like for the sentence regarding "Race": to stand.

FDA response: The division does not agree that the information provided is adequate to support a sentence regarding race, and therefore would like to maintain proposed that: The effect of race on the pharmacokinetics of Fem HRT has not been studied.

4. The sponsor would like to add [redacted] ratios to Table 4: "Mean % change from baseline lipid profile".

FDA response: The division does not find this compatible with class labeling for HRT products and therefore is not in favor of [redacted] ratios or any lipid ratios that may infer cardiac benefit.

5. The sponsor would like to add under **INDICATIONS AND USAGE** section #4. Prevention and management of osteoporosis.

FDA response: This is a review issue for DMEDP, however, this statement is not compatible with class labeling for HRT products seeking an osteoporosis indication and may be found to be unacceptable.

6. The sponsor would like to add a statement under the **WARNING** section, subheading #1. **Endometrial Cancer** to read:
"There is no evidence that natural estrogens are more or less hazardous than synthetic estrogens at equivalent doses".

FDA response: DDMAC reports that this is a true statement and will allow it in the label.

7. The sponsor would like to keep a paragraph under the **WARNING** section, subheading #2 **Breast Cancer** section, that [redacted]

FDA response: The division is not in favor of this comparison.

Action Item:

- Sponsor to submit in writing full label comments for teleconference September 10, 1999.
Received by secured e-mail evening of
September 9, 1999
- Distribute comments from sponsor to reviewers for teleconference September 10, 1999
Reviewers received labeling comments
September 10, 1999 a.m. prior to meeting

Note: Letter from sponsor withdrawing [redacted] from NDA 21-065 received September 28, 1999.

[redacted] /S/

Minutes Preparer

[redacted] /S/

Chair Concurrence

10/12/99

Cc: Original

HFD/Div Files

HFD-580/Spell-Lesane

HFD-580/Rarick/Mann/Davis/Slaughter/Rhee/Ortwerth/Jordan/Parekh/Jarugula/
Kammerman/Hoberman/

Concurrence: Rumble, 9.30.99, Ortwerth, 10.01.99, Mann, 10.4.99

Draft: September 28, 1999

Final: Spell-LeSane, 10.11.99

APPEARS THIS WAY
ON ORIGINAL

MINUTES of TELECONFERENCE

Date: August 31, 1999

Time: 11:30 - 11:50 AM

Location: Parklawn; 17B-43

NDA: 21-065

Drug Name: FemHRT [] ethinyl estradiol (EE) []
norethindrone acetate (NETA)] tablets

Indication: Hormone replacement therapy (HRT)

External Participant: Parke-Davis

Type of Meeting: Guidance (labeling)

Meeting Chair: Dr. Daniel Davis

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Dan Davis, M.D., - Medical Officer, Division of Reproductive and Urologic Drug
Products (DRUDP; HFD-580)

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

External Constituents:

Mary Taylor - Director, Regulatory Liaison

Ross Lobel - Senior Manager, Regulatory

Jim Symons, Ph.D. - Director, Clinical Research

Richard Hanley - Senior Director, Clinical Research

Meeting Objectives: To discuss the proposed draft labeling regarding the indications and the efficacy of the lowest dose.

Background: A meeting is scheduled between the Division and the sponsor on September 10, 1999.

Discussion Points:

- the sponsor's labeling comments were received on August 27, 1999
- amenorrhea data were taken only during clinic visits and were not recorded in the early diaries; none were recorded on a monthly basis; the sponsor feels that the data is not complete enough to be used as the cumulative amenorrhea chart data; an on-going study is using daily diaries which may have data that could be useful for this purpose
- the Agency feels that in order for the amenorrhea data in the labeling to be useful to the practitioner, it should incorporate information of at least 12-months duration; 12-week data (3 month) is not adequate for cumulative amenorrhea data in the labeling
- the 12-week study was considered by the Division to be pivotal because it contained women who had a minimum of 50 hot flushes per week
- these comments are preliminary as the review of the patient labeling has not been completed; future comments are expected and will be communicated

Decisions reached:

- Figure 3. entitled, [redacted] should be deleted
- [redacted]
- in the **DOSAGE AND ADMINISTRATION** section, previously the [redacted] indication was combined with the vasomotor (VMS) indication; however, no studies were performed with endpoints adequate for evaluating the [redacted] indication (no biopsies or maturation indexes were submitted); therefore, the [redacted] indication should not be included in the label
- the proposed endpoint of [redacted] that was included in the osteoporosis trial is not an adequate endpoint for [redacted]
- 12-month data showing cumulative amenorrhea should be shown in the label

Action Items:

- | Item: | Responsible Person | Due Date: |
|-----------------------------------|--------------------|-----------|
| • provide copy of Telecon minutes | Ms. Moore | 1 month |

[redacted] /S/ 9/13/99
Signature, minutes preparer

[redacted] /S/
Concurrence, Chair

drafted: dm/September 2, 1999/N21065TC83199.doc

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/DDavis/DSpell-Lesane
HFD-580/D Moore

Concurrence:
TRumble 09.07.99/DDavis

APPEARS THIS WAY
ON ORIGINAL

OCT 12 1999

MEETING MINUTES

Date: August 18, 1999

Time: 9:00-10:00 a.m.

Location: Parklawn; 17B43

NDA: 21-065

Drug: Fem HRT (Norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy/Osteoporosis

Type of meeting: 8-Month Status (internal)

FDA lead: Dr. Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

Venkat Jarugula, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, ONDCII, @ DRUDP (HFD-580)

Davis Hoberman, Ph.D. Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)

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

Joanne Zawadzki, M.D., Medical Officer, Division of Metabolic and Endocrine Drug Products, (DMEDP; HFD-510)

Meeting Objective

To discuss the status of reviews for NDA 21-065

Discussion

Clinical pharmacology:

- review for four studies have been completed
- population PK data to be reviewed which will have information that will impact the label

Clinical:

DMEDP:

- **Indications and Usage** text of the label will be reviewed for osteoporosis implications

DRUDP:

- patient biopsy reports will be a review issue

Chemistry:

- review is under final review by Team Leader
- information request letter to sponsor is needed to convey deficiencies

▪ **Action Items:**

- Send information request letter to Parke-Davis regarding chemistry deficiencies
(Letter sent August 27, 1999)
- DMEDP to consult DDMAC regarding labeling for osteoporosis
- reviews should be completed by Division goal date October 3, 1999

/S/

Minutes Preparer

/S/

Chair Concurrence

10/12/99

Cc: Original

HFD/Div Files

HFD-580/Spell-Lesane

HFD-580/Rarick/Mann/Davis/Slaughter/Rhee/Ortwerth/Jordan/Parekh/
Kammerman/Hoberman/

Draft: 9.30.99

concurrence: Rumble, 9.30.99, Mann, 10.4.99, Zawadzki, 10.4.99

Final: Spell-LeSane, 10.11.99

APPEARS THIS WAY
ON ORIGINAL

OCT 12 1999

MEETING MINUTES

Date: July 26, 1999

Time: 3:00 -4:00p.m.

Location: Parklawn; 17B45

NDA: 21-065

Drug: FemHRT (Norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement Therapy

Type of meeting: 7 Month Status

FDA lead: Dr. Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

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

Joanne Zawadzki, M.D. Medical Officer, Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

Vanketesar Jarugula, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

Michael Ortwerth, Ph. D., Chemistry Reviewer, ONDC II, @ DRUDP (HFD-580)

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

Meeting Objective

To discuss the status of reviews for NDA 21-065

Background:

This NDA is currently under review by this division with a 10-month goal date of October 17, 1999. NDA 21-102 is concurrently under review by DMEDP for an osteoporosis indication.

Discussion

Clinical pharmacology:

- three studies have been reviewed, with three additional studies pending review completion
- food effect study: food decreases C_{max} by 29% and increases AUC of NE by 27%; this may need to be reflected on the label, although clinical studies were done without regard to food intake.

• [REDACTED]

Pharm Tox:

- review is completed; recommended approval

Clinical:

- review is pending

Chemistry:

- Duramed requested a [] month expiration date, 18-month expiration may possibly be granted
- drug substance supplier will need to update type I DMF to include drug substance storage data
- inhomogeneties have been identified in reviewing manufacturing methods
- friability testing is not included as an in-process control
- data has been submitted that is supportive to Duramed data and an updated Duramed data sheet will be submitted in September. This submission may need to be a major amendment
- inspections for [] due August 1, 1999
- the following comments were conveyed to the sponsor June 11, 1999 via t-con between Dr. Ortwerth and the sponsor

Background:

On 21-MAY-1999, Shawn Brennon and Len Lescosky contacted Chemistry to request that their specifications for Content/Uniformity testing of their Drug Product be reviewed and respond with comments. The sponsor was prompted to request chemistry comments due to a concurrent review of their Drug Product in the [] in which the [] has challenged their Content/Uniformity specifications. On June 11, 1999, the sponsor contacted Dr. Ortwerth and commented on his review of their Content/Uniformity specifications.

Comments to the sponsor

Sponsor should consider:

1. Providing limits for Relative Standard Deviations (RSDs) in all tiers of testing.
2. Reducing the upper limit of [] in the range for first and second tier testing of Ethinyl Estradiol where the condition of no unit out of range is set.
3. Providing a detailed explanation for their use of specifications that deviate from the United States Pharmacopoeia(USP).
4. Establishing Release specifications as well as standard marketed Drug Product specifications.

The sponsor seemed very willing to address these issues and it was requested that an Amendment to the NDA that would give further clarity and justifications to the issues be submitted.

Biometrics

- will review as needed at request of Medical Officer

510 Clinical for Osteoporosis indication

- DMEDP is in receipt of volumes requested from the sponsor 7/8/99; review is pending
- DMEDP will be reviewing two studies looking at vasomotor symptoms and a 2-yr study where patients received a calcium supplement

Decision Reached:

- DMEDP (HFD 510) MO and PM will contact sponsor for labeling issues and general request for information related to the osteoporosis indication
- DMEDP aware of User Fee goal date of October 17, 1999 and agrees to aim for both applications to be acted on simultaneously

Action Items:

- copies of disc that contains draft labeling to be distributed to all reviewers by the end of the day (Completed 7/26/99)
- add labeling as an agenda item for next meeting September 8, 1999 (Completed 7/26/99)

/S/

Minutes Preparer

/S/

Chair Concurrence

10/12/99

Cc: Original
HFD/Div Files
HFD-580/Spell-LeSane
HFD-580/Rarick/Mann/Price/Slaughter/Rhee/Mitra/Jordan/Parekh/
Kammerman/Hoberman/

Draft: Spell-LeSane 7.26.99
concurrence: Rumble, 9.30.99, Ortwerth, 10.01.99, Zawadzki, 10.4.99, Mann, 10.7.99

Final: Spell-LeSane, 10.11.99

MEETING MINUTES

MEETING MINUTES

OCT 12 1999

Date: June 9, 1999

Time: 9:00-10:00 a.m.

Location: Parklawn; 17B-43

NDA: 21-065

Drug: Fem HRT (Norethindrone acetate and ethinyl estradiol)

Sponsor: Parke-Davis Pharmaceutical Research

Indication: HRT (treatment of vasomotor symptoms, [redacted] and osteoporosis)

Type of meeting: 6-month status (internal)

FDA lead: Dr. Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

Participants:

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP HFD-580)

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

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

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

Venkat Jarugula, Ph.D., Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD 580)

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

Meeting Objective

To discuss the status of reviews for NDA 21-065.

Background:

This NDA dated December 16, 1998 received December 17, 1998, has a user fee goal date of October 17, 1999 and a secondary user fee goal date of December 17, 1999. This NDA is also seeking an indication for osteoporosis and will be unbundled and reviewed by the Division of Metabolic and Endocrine Drug Products; (HFD-510).

Discussion

Clinical:

- review is pending
- data for osteoporosis indication will be reviewed by DMEDP
- Estrostep and Activelle may be used as reference and comparisons for labeling
- one DSI site has been complete/VAI

Clinical pharmacology:

- review is pending

Pharm Tox:

- review is completed; recommended approval

Chemistry:

- deficiencies have been identified
- results indicate that there may be an override of ethinyl estradiol
- one DMF was withdrawn and the DMF holder has been informed of the withdrawal status
- DMF for child resistant closures have been requested
- 12-month stability data from Duramed had been discussed including launch material
- follow up is in progress regarding the drug substance for this product (Parke Davis outsources to [redacted] who outsources to sister company [redacted] who stores the drug substances and transfers the compounds to Duramed to formulate the tablets).

Action Items:

- contact Enid Galliers regarding status of type 6 NDA in DMEDP

inquiry sent June 10, 1999 to the DMEDP June 29, 1999, #21-102 was assigned to the type 6 NDA

- invite MO from DMEDP to next status meeting

Dr. Joan Zawadzki identified as MO from DMEDP and invited to all scheduled status meetings

- schedule two internal labeling meetings

Status meetings scheduled for July 26, and August 18, 1999

- schedule two labeling meetings with sponsor

Labeling meetings with sponsor scheduled for September 8, & 17, 1999.

/S/

Minutes Preparer

/S/

Chair Concurrence

10/12/99

Teleconference Minutes

APR 05 1999

Date: April 5, 1999 **Time:** 9:00-9:15 a.m. **Location:** Parklawn; Rm. 17B-43

NDA: 21,065 **Drug:** Fem HRT (Norethindrone acetate and ethinyl estradiol)

Indication: Hormone Replacement therapy

Sponsor: Parke-Davis Pharmaceutical

Type of Meeting: Request for Waiver

Meeting Chair: Dan Davis, MD, Medical Officer, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

External Lead: Robin Pitts, Manager, FDA Liaison

Meeting Recorder: Dornette Spell-LeSane, NP-C, Regulatory Project Manager

FDA Attendees:

Dan Davis, M.D. - Medical Officer, Division of Reproductive and Urologic Drug Products, DRUDP, (HFD-580)

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

External Attendees:

Robin Pitts, Manager, FDA Liaison

Meeting Objective:

To respond to a request from the sponsor dated March 30, 1999, for a waiver from submitting CRF's for patients who withdrew from a study due to adverse events (ADEs); this waiver would allow the sponsor to not submit CRF's as part of the 4-month safety update (SU) for protocol 376-401.

Background:

The NDA was submitted December 16, 1998. The protocol in question, "A Randomized Double Blind Active and Placebo-Controlled, Parallel Group, Multicenter Study Assessing Safety and Protective Effect on Endometrium of 4 Dosage combinations of Norethindrone Acetate plus Ethinyl Estradiol", was initiated in February 1998, is ongoing and remains blinded. The sponsor had questions regarding the submission of ADEs for the 4-month safety review due in April. It was recommended that the sponsor submit a request for a waiver in writing.

Discussion:

Dr. Davis reviewed with Ms. Pitts 1) the purpose of the study, 2) the total number of patients in the study and, 3) the number of patients who had withdrawn due to adverse events. It was determined that it was necessary to submit the case report forms for those participants.

NDA, 21-065
Teleconference minutes 4/5/99
Page 2

Decisions made:

- The waiver was denied
- CRF's for the dropouts due to ADEs must be submitted with the Safety Update

Unresolved decisions:

None

Action Items:

- a complete 4-month Safety Update is due as scheduled
- minutes will be exchanged with the sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

4/8/99

cc:

Original NDA 21-065

HFD-580/DivFile

HFD-580/Spell-LeSane

HFD-580/Rarick/Mann/Slaughter/Davis/Jordan/Rhee/Parekh/Kammerman/Ortwerth

drafted: dsl, 4/7/99, NDA 21,065

concurrence: Rumble, 4.7.99/Davis, 4.7.99

final: Spell-LeSane, 4.8.99

TELECONFERENCE MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Minutes

Date: January 19, 1999

Time: 1:00 – 2:00 PM

Location: Parklawn; 17B-43

NDA 21-065

Drug: FemHRT

Indication: HRT

Sponsor: Parke Davis Pharmaceuticals

Type of Meeting: Filing Meeting

Meeting Chair: Lisa Rarick, M.D.- Division Director

Meeting Recorder: Jennifer Mercier, Project Manager

FDA Attendees:

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

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

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

Michael Ortwerth, Ph.D. - Chemist, (DNDCII) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. – Statistics Team Leader, Division of Biometrics II (DBII; HFD-715) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Biopharmaceutics Team Leader, Division of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)

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

Shelley Slaughter, M.D. – Acting Team Leader, DRUDP (HFD-580)

Terri Rumble, B.S.N. – Project Manager, DRUDP (HFD-580)

Jennifer Mercier, Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the fileability of this application

Discussion:

- Pharmacology
 - the application is fileable
- Clinical
 - the application is fileable; consult HFD-510 for the osteoporosis indication
- Statistical
 - the application is fileable
- Clinical Pharmacology
 - the application is fileable


FEB 12 1999

- Chemistry
 - the application is fileable

Decisions made: this application is fileable pending the review from HFD-510

Action Items:

- Consult HFD-510 for the osteoporosis indication and the fileability of the application from that perspective; the medical officer from 510 is Dr. Joanna Zawadzki
- Request sponsor to submit the statistical results by center


Minutes Preparer


Concurrence, Chair

Post Meeting Note:

- This NDA is being split administratively into a Type 6 NDA for the osteoporosis indication. The consult is no longer valid. HFD-510 will review the osteoporosis indication.

cc:

Original NDA

HFD-580/DivFile

HFD-580/PM/Rumble/Pauls/Mercier

HFD-580/Rarick/Mann/Davis/Slaughter/Jordan/Rhee/Ortwerth/ Parekh/ Jarugula/Kammerman

drafted:

concurrence:

final:

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

IND [redacted]

Norethindrone Acetate & Ethinyl Estradiol
Parke-Davis

September 22, 1992

DIV

Memorandum of Meeting

Industry Representatives:

Debra Gmerek, Ph.D., Clinical Communications
Irwin Martin, Ph.D., Regulatory Affairs
William Merino, Ph.D., Regulatory Affairs
Jean Rowan, M.D., Clinical Development
James Symons, M.S., Clinical Development
Mary Taylor, Regulatory Affairs
Julie Wu, Ph.D., Biometrics

FDA Staff:

Dr. Sobel	Dr. Stadel
Dr. Troendle	Dr. S. Dutta
Dr. Corfman	Dr. Dorantes (HFD-426)
Dr. Golden	Mr. Marticello (HFD-713)
Dr. Bennett	Ms. Olmstead

Purpose: Pre-NDA meeting.

Discussion and Conclusions:

The firm is planning to submit an NDA in June 1993 with the proposed indications: treatment of moderate-to-severe vasomotor symptoms associated with menopause and [redacted]. An amendment for the prevention of osteoporosis indication is planned for June 1994.

Studies 376-343 and 376-368

The firm intends to submit the hot flush frequency data from studies 376-343 and 376-368 in support of the treatment of vasomotor symptoms indication. The Agency will not approve a vasomotor symptom indication unless the firm provides data to support the reduction in both intensity and frequency of hot flashes. The firm should review the data in studies 376-343 and 376-368 for variables that would support the reduction in severity/intensity of the hot flashes. The Agency also requested that the firm define moderate-to-severe hot flashes when presenting their analysis.

The firm was requested to review the data regarding a possible relationship between the dose and body weight since the amount of endogenous estrogen produced may determine the exogenous amount needed. The firm will also provide information on the weight criterion for entry.

The NDA will be submitted with 2 dosages proposed for the treatment of vasomotor symptoms, [redacted]

Study 376-359

Studies 376-368 and 376-359 will be submitted to support the proposed indications for prevention of osteoporosis and [REDACTED]

The Agency indicated that proliferative endometrium is not an acceptable primary endpoint. Hyperplasia is the only acceptable surrogate for endometrial cancer. The classification/criteria for reading biopsies should reflect those found in Blaustein's Pathology of the Female Genital Tract, 1987, Chapter 11.

The Agency indicated that presenting a descriptive analysis for lipids and vaginal bleeding is acceptable but for the bone mineral density data it is not adequate.

The early termination of a treatment group will cause the firm to take a statistical penalty for one-year endometrial analysis.

If the firm intends to submit the NDA prior to the completion of study 376-359, the blinding-codes must be submitted by the 45-day meeting. The Division will not file the application without the codes. Alternatively, the firm was advised it would be preferable to defer NDA submission until all studies are complete.

The firm intends to submit a 4-month safety update following the NDA submission.

/S/

Sharon Olmstead, CSO

ATTACHMENTS
Overheads

APPEARS THIS WAY
ON ORIGINAL

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

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]. 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:

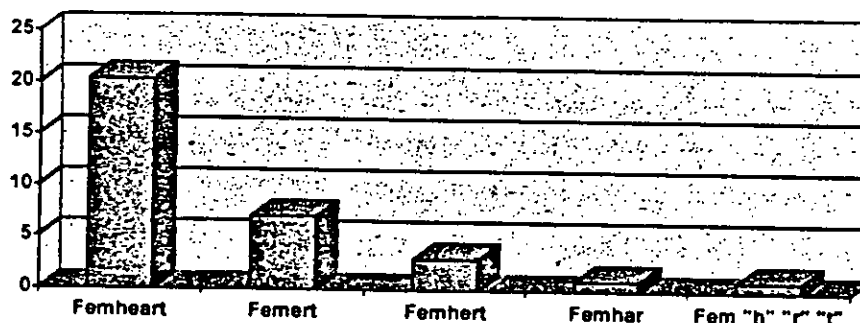
1. An internal study was conducted within OPDRA to evaluate the proposed proprietary name and determine how the proposed name would be pronounced. This analysis was conducted to determine if the new presentation of the name would still have the connotation of "heart" associated with it.

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, [] 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

Memorandum to File

To: NDA 21102 (NDA 21065 in Division of Reproductive and Urologic Drug Products)

From: Joanna K. Zawadzki, M.D. [redacted] /S/
Medical Officer
Division of Metabolic and Endocrine Drug Products [redacted] /S/

Subject: Breast Cancer Ascertainment in NDA Medical Officer Review

Date: 11/3/99

In the NDA medical officer review, this medical officer had raised a concern about the number of breast cancers in patients treated with norethindrone acetate ethinyl estradiol (NA/EE) as compared to the numbers of breast cancers in patients treated with placebo. To evaluate this issue further, the breast cancer data were discussed with epidemiologist Bruce Stadel, M.D., M.P.H. and rates of breast cancer in the different study arms were compared. (See attached table.) 4/566 patients on NA/EE were diagnosed with breast cancer versus 0/137 patients on placebo in Study 376-359 ($p=.4193$, by Fisher's exact test.) Study 376-343 is more difficult to analyze as it was an open-label study, but 3/41 on NA/EE vs. 0/10 on placebo is also not significant [$p=.5119$ by Fisher's exact test.] Also, if the two studies are stratified, $p=.35$. Thus, it is difficult to discern a significant difference in the ascertainment of breast cancer between the randomized drug and placebo groups. These findings do not raise concern that the relationship between this drug and breast cancer is different from other studies of estrogen and breast cancer.

APPEARS THIS WAY
ON ORIGINAL

Number (%) of Subjects in Osteoporosis Studies and Breast Cancer Ascertainment
(adapted from Tables 7 [ISS p. 26 of 86], Table 12 [ISE p.38 of 162], App. C 4-6 [pp662-4])

^a The 10 mcg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia.

Study	Placebo	Fem HRT (mgNA/EEmcg)							total Fem HRT	EE (mcg)				Total EE	MPA /CEE	Total
		0.2/1	.5/2.5	0.5/5	1/5	.5/10	1/10	1/20		1	2.5	5	10 ^a			
376-343 Randomized	10			12	14	13	14	12	65						12	87
At 12 months	10			11	10	12	13	11							8	
Open-label	5			9	9	11	13								4	
Year 5	5			9	7	9	12								1	
# Patients with Breast Cancer (study day)					1 (1487)	1 (7)	1 (773)									
376-359 Randomized	137	139	136		146		145		566	141	137	141	143	562		1265
Intent To Treat (ITT)	123 (90)	119 (86)	120 (88)		124 (85)		118 (81)			119 (84)	119 (88)	121 (86)	101 (71)			1065 (84)
Observed at 12 months	109 (80)	105 (76)	110 (81)		111 (76)		105 (72)			108 (77)	111 (81)	112 (79)	60 (42)			931 (74)
Observed at 24 months	97 (71)	99 (71)	99 (73)		102 (70)		98 (68)			96 (68)	92 (67)	105 (74)	14 (10)			802 (65)
Evaluable at 12 months	98 (72)	94 (68)	93 (68)		96 (66)		92 (63)			92 (65)	96 (70)	99 (70)	51 (36)			811 (64)
Evaluable at 24 months	86 (63)	86 (62)	85 (62)		89 (61)		88 (61)			81 (57)	80 (58)	90 (64)	10 (7)			695 (55)
# Patients with Breast Cancer (study day)	0	1 (201)	1 (143)		1 (552)		1 (393)			1 (714)	1 (380)	0	1 (367)			

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] [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 (femhrtTM) 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.

**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

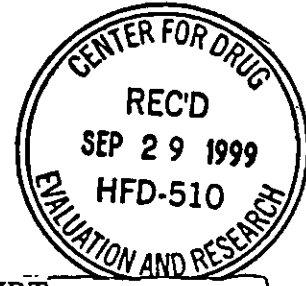
The Team Leader's signature on the medical review replaces this memorandum.

**APPEARS THIS WAY
ON ORIGINAL**

 **PARKE-DAVIS**

September 28, 1999

NDA 21-102
Ref. No. 001
FemHRT



Re: Withdrawal of FemHRT [redacted]

[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.

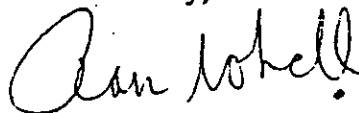
Therefore, we request that the FemHRT [redacted] be withdrawn from both NDA 21-065 and 21-102 without prejudice. We wish to continue ongoing registration activities for the FemHRT 1/5 and [redacted] tablet strengths and look forward to the completion of the Agency's review of these two dose strengths.

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.

APPEARS THIS WAY
ON ORIGINAL

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

"Win-14Secure 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.

=====

APPEARS THIS WAY
ON ORIGINAL

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
TO: Joanna Zawadzki

(galliers@A1)
(zawadzki@A1)

Subject: NDA 21-102

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:

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

=====

APPEARS THIS WAY
ON ORIGINAL

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**

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: 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

**APPEARS THIS WAY
ON ORIGINAL**

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

**APPEARS THIS WAY
ON ORIGINAL**

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>