CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-065

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21065/000
Stamp: 17-DEC-1998
Regulatory Due: 17-OCT-1999
Applicant: PARKE DAVIS
2800 PLYMOUTH RD
ANN ARBOR, MI 48105
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 18-AUG-1999
Brand Name: FEMHRT (ETHINYL ESTRADIOL/NORETHINDRONE A
Estab. Name:
Generic Name: ETHINYL ESTRADIOL/NORETHINDRONE ACETATE

Dosage Form: (TABLET)
Strength: [redacted] 5/1 [redacted] UGM/MG

Application Comment: THIS SUBMISSION IS A NEW NDA FOR HORMONE REPLACEMENT THERAPY USING EE AND NA IN NEW COMBINATIONS FOR USE IN WOMEN WITH INTACT UTERI FOR THE TREATEMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE, [redacted] AND PREVENTION OF OSTEOPEROSIS. (on 28-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

FDA Contacts:
J. MERCIER (HFD-580) 301-827-4260 , Project Manager
M. ORTWERTH (HFD-580) 301-827-4260 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 01-OCT-1999 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: RESPONSIBLE FOR RELEASE AND STABILITY TESTING OF DRUG PRODUCT. (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
OC RECOMMENDATION	29-JAN-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 1526814
DURAMED PHARMACEUTICALS INC
5040 LESTER RD
CINCINNATI, OH 45213

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE
Estab. Comment: RESPONSIBLE FOR (1) TESTING, APPROVAL, AND RELEASE OF DRUG SUBSTANCE AND COMPONENTS, (2) MANUFACTURING, PACKAGING, AND LABELING OF DRUG PRODUCT, AND (3) APPROVAL AND RELEASE OF DRUG PRODUCT. (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
SUBMITTED TO DO	29-JAN-1999	10D			FERGUSONS
ASSIGNED INSPECTION	14-JUN-1999	PS			JLUBBERS
INSPECTION SCHEDULED	27-JUL-1999		04-AUG-1999		DGRELLE
INSPECTION PERFORMED	11-AUG-1999		05-AUG-1999		DGRELLE

PRODUCT SPECIFIC PREAPPROVAL INSPECTION FOUND FIRM IS CAPABLE OF MANUFACTURING THIS PRODUCT IN CONFORMANCE WITH THE NDA AND GMP COMMITMENTS.

DO RECOMMENDATION	11-AUG-1999	ACCEPTABLE INSPECTION	DGRELLE

PRODUCT SPECIFIC PREAPPROVAL INSPECTION FOUND DURAMED IS CAPABLE OF MANUFACTURING THIS PRODUCT PER THE NDA AND GMP REQUIREMENTS

OC RECOMMENDATION	11-AUG-1999	ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: MANUFACTURER OF DRUG SUBSTANCES ETHINYL ESTRADIOL AND NORETHINDRONE ACETATE (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
SUBMITTED TO DO	29-JAN-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	02-FEB-1999	GMP			EGASM
INSPECTION PERFORMED	01-OCT-1999		14-MAY-1999		FERGUSONS
DO RECOMMENDATION	01-OCT-1999			ACCEPTABLE INSPECTION	FERGUSONS
OC RECOMMENDATION	01-OCT-1999			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-MAY-1999				EGASM
OC RECOMMENDATION	10-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER

Profile: CRU OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

SUBMITTED TO OC	10-MAY-1999		EGASM
SUBMITTED TO DO	10-MAY-1999 GMP		EGASM
ASSIGNED INSPECTION	10-MAY-1999 GMP		EGASM
DO RECOMMENDATION	01-OCT-1999	ACCEPTABLE	FERGUSONS
		BASED ON FILE REVIEW	
OC RECOMMENDATION	01-OCT-1999	ACCEPTABLE	FERGUSONS
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

NDA: 21-065

Drug Northindrone acetate/ethinyl estradiol

Sponsor: Parke-Davis

Date: 10/14/99

Microbiology Review not applicable for this NDA

APPEARS THIS WAY
ON ORIGINAL

NDA 21-065

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21065/000
Stamp: 17-DEC-1998
Regulatory Due: 17-OCT-1999
Applicant: PARKE DAVIS
2800 PLYMOUTH RD
ANN ARBOR, MI 48105
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 18-AUG-1999
Brand Name: FEMHRT(ETHINYL ESTRADIOL/NORETHINDRONE A
Estab. Name:
Generic Name: ETHINYL ESTRADIOL/NORETHINDRONE ACETATE

Dosage Form: (TABLET)
Strength: [redacted] 5/1 [redacted] UGM/MG

Application Comment: THIS SUBMISSION IS A NEW NDA FOR HORMONE REPLACEMENT THERAPY USING EE AND NA IN NEW COMBINATIONS FOR USE IN WOMEN WITH INTACT UTERI FOR THE TREATEMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE, [redacted] AND PREVENTION OF OSTEOPEROSIS. (on 28-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

FDA Contacts: J. MERCIER (HFD-580) 301-827-4260 , Project Manager
M. ORTWERTH (HFD-580) 301-827-4260 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE
Estab. Comment: RESPONSIBLE FOR RELEASE AND STABILITY TESTING OF DRUG PRODUCT. (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
OC RECOMMENDATION	29-JAN-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 1526814
DURAMED PHARMACEUTICALS INC
5040 LESTER RD
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DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE
Estab. Comment: RESPONSIBLE FOR (1) TESTING, APPROVAL, AND RELEASE OF DRUG SUBSTANCE AND COMPONENTS, (2) MANUFACTURING, PACKAGING, AND LABELING OF DRUG PRODUCT, AND (3) APPROVAL AND RELEASE OF DRUG PRODUCT. (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
SUBMITTED TO DO	29-JAN-1999	10D			FERGUSONS
ASSIGNED INSPECTION	14-JUN-1999	PS			JLUBBERS
INSPECTION SCHEDULED	27-JUL-1999		04-AUG-1999		DGRELLE
INSPECTION PERFORMED	11-AUG-1999		05-AUG-1999		DGRELLE

PRODUCT SPECIFIC PREAPPROVAL INSPECTION FOUND FIRM IS CAPABLE OF MANUFACTURING THIS PRODUCT IN CONFORMANCE WITH THE NDA AND GMP COMMITMENTS.
DO RECOMMENDATION 11-AUG-1999 ACCEPTABLE DGRELLE
INSPECTION

PRODUCT SPECIFIC PREAPPROVAL INSPECTION FOUND DURAMED IS CAPABLE OF MANUFACTURING THIS PRODUCT PER THE NDA AND GMP REQUIREMENTS
OC RECOMMENDATION 11-AUG-1999 ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: MANUFACTURER OF DRUG SUBSTANCES ETHINYL ESTRADIOL AND NORETHINDRONE ACETATE (on 27-JAN-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-1999				ORTWERTHM
SUBMITTED TO DO	29-JAN-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	02-FEB-1999	GMP			EGASM

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-MAY-1999				EGASM
OC RECOMMENDATION	10-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MICRONIZER
Profile: CRU OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-MAY-1999				EGASM
SUBMITTED TO DO	10-MAY-1999	GMP			EGASM
ASSIGNED INSPECTION	10-MAY-1999	GMP			EGASM

ITEM 13
PATENT AND MARKET EXCLUSIVITY INFORMATION

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

13.1. Patent Information

NDA Number:	21-065
Applicant:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48106
Active Ingredient:	HRT is a 1:1 ratio of ethinyl estradiol and norethindrone acetate. The empirical formula of HRT is $C_{20}H_{24}O_2$ (ethinyl estradiol) and $C_{22}H_{28}O_3$ (norethindrone acetate) and the molecular weight is 636.87.
Medical Use:	HRT is continuous orally administered combination of norethindrone acetate/ethinyl estradiol for prevention of osteoporosis and treatment of hypoestrogenic states, especially those associated with the perimenopause, menopause, and following oophorectomy.
Strength:	[redacted] 1 mg norethindrone acetate/5 µg ethinyl estradiol [redacted]
Dosage Form:	Tablet

Trade Name: FemHRT™

Generic Name: norethindrone acetate/ethinyl estradiol
Patent Statement: One patent covers HRT

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

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

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

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # _21-065__ SUPPL #_____

Trade Name _femhrt_ ___ Generic Name: northindrone/acetate/ethinyl estradiol _

Applicant Name __Parke-Davis HFD # 580_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

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

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

YES /X/ NO /___/

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

_____

_____

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

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_x__/ NO /___/

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

3

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

_____no_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /_X__/ NO /___/

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

NDA# 017355 _Loestrin_____

NDA# _017565_ Norinyl_____

NDA# _017488__ Modicon_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

APPEARS THIS WAY
ON ORIGINAL

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

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

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

YES /X__/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

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

YES /___/ NO /_X_/

If yes, explain:

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

YES /___/ NO /_X_/

If yes, explain:

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

376-390

376-359

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

APPEARS THIS WAY
ON ORIGINAL

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

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

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

Investigation #1 YES /_ _/ NO /_X_/

Investigation #2 YES /_ _/ NO /_X_/

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

_____ _____

_____ _____

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

____376-368 _____

__376-343_ _____

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 !

IND # [ ] YES/X NO/___/ Explain: _____

Investigation #2 !

IND # [ ] YES/X NO /___/ Explain: _____

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

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

APPEARS THIS WAY
ON ORIGINAL

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature /S/ Date 10/7/99
Regulatory Project Manager

/S/ 10/15/99
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

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 [redacted] under which the clinical investigation identified in 2 above was performed.

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21065	**Trade Name:**	FEMHRT(ETHINYL ESTRADIOL/NORETHINDRONE A
Supplement Number:		**Generic Name:**	ETHINYL ESTRADIOL/NORETHINDRONE ACETATE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	treatment of vasomotor symptoms in postmenopausal women

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status

Studies Needed

Study Status

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

COMMENTS:

This drug is used in the postmenopausal age group and does not have pediatric implications

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DORNETTE SPELL-LESANE

/S/

Signature

10/1/99

Date

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert Company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

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

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

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

COMMENTS:

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

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

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

/S/

Signature

10.15.99

Date

FemHRT NA-EE
Tablets

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert Company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Exclusivity Checklist

NDA: 21-102 (osteoporosis prevention indication unbundled from NDA 21-065)				
Trade Name: femhrt™				
Generic Name: 1mg NORETHINDRONE ACETATE/5mcg ETHINYL ESTRADIOL tablets				
Applicant Name: PARKE DAVIS PHARMACEUTICAL RESEARCH				
Division: 510 DMEDP				
Project Manager: ENID GALLIERS				
Approval Date: 15-OCT-1999				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	✓	No	
b. Is it an effectiveness supplement?	Yes		No	✓
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	✓	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	3			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	_	No	✓
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE				

BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	✓
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes	✓	No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	✓	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	✓	No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes	_	No	✓
If yes, explain:				

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: 376-359				
Investigation #2, Study #: —				
Investigation #3, Study #: —				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2 N/A	Yes		No	
Investigation #3 N/A	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2 N/A	Yes		No	
Investigation #3 N/A	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1 376-359				

Investigation #2 N/A					
Investigation #3 N/A					
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.					
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?					
Investigation #1 376-359	Yes	✓	No		
IND#:					
Explain:					
Investigation #2 —	Yes		No		
IND#:					
Explain:					
Investigation #3 —	Yes		No		
IND#:					
Explain:					
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A					
Investigation #1	Yes		No		
IND#:					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		
IND#:					
Explain:					
c. Notwithstanding an answer of "yes" to (a) or (b), are there					

other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

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Signature of PM/CSO

APPEARS THIS WAY
ON ORIGINAL

ITEM 13
PATENT AND MARKET EXCLUSIVITY INFORMATION

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

13.1. Patent Information

NDA Number:	21-065
Applicant:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48106
Active Ingredient:	HRT is a 1:1 ratio of ethinyl estradiol and norethindrone acetate. The empirical formula of HRT is $C_{20}H_{24}O_2$ (ethinyl estradiol) and $C_{22}H_{28}O_3$ (norethindrone acetate) and the molecular weight is 636.87.
Medical Use:	HRT is continuous orally administered combination of norethindrone acetate/ethinyl estradiol for prevention of osteoporosis and treatment of hypoestrogenic states, especially those associated with the perimenopause, menopause, and following oophorectomy.
Strength:	[redacted] 1 mg norethindrone acetate/5 µg ethinyl estradiol [redacted]
Dosage Form:	Tablet

Trade Name: FemHRT™

Generic Name: norethindrone acetate/ethinyl estradiol
Patent Statement: One patent covers HRT

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

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

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