CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-065

CHEMISTRY REVIEW(S)

NDA 21-065 Sponsor: Parke-Davis Drug: Norethindrone acetate/Ethinyl estradiol

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

OCT 14 1999

NDA #: 21-065 **DATE REVIEWED:** 14-OCT-1999

REVIEW #: 2 **REVIEWER:** Michael Ortwerth

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	24-JUN-1999	25-JUN-1999	28-JUN-1999
AMENDMENT	03-SEP-1999	07-SEP-1999	08-SEP-1999
AMENDMENT	17-SEP-1999	21-SEP-1999	21-SEP-1999
AMENDMENT	28-SEP-1999	29-SEP-1999	04-OCT-1999
AMENDMENT	28-SEP-1999	29-SEP-1999	04-OCT-1999
AMENDMENT	29-SEP-1999	29-SEP-1999	29-SEP-1999
AMENDMENT	01-OCT-1999	01-OCT-1999	01-OCT-1999
AMENDMENT	08-OCT-1999	09-OCT-1999	13-OCT-1999
AMENDMENT	12-OCT-1999	13-OCT-1999	13-OCT-1999
AMENDMENT	13-OCT-1999	14-OCT-1999	14-OCT-1999

NAME & ADDRESS OF APPLICANT:

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106-1047

DRUG PRODUCT NAME

Proprietary: FemHRT
Established: Norethindrone acetate (NA) and Ethinyl estradiol (EE)
Code Name/#: CI-376
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY/INDICATION: Progestin/Estrogen / Hormone Replacement Therapy

DOSAGE FORM: Tablets
STRENGTHS: 1 mg NA/5 µg EE

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: X Rx __ OTC

SPECIAL PRODUCTS: __ Yes X No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

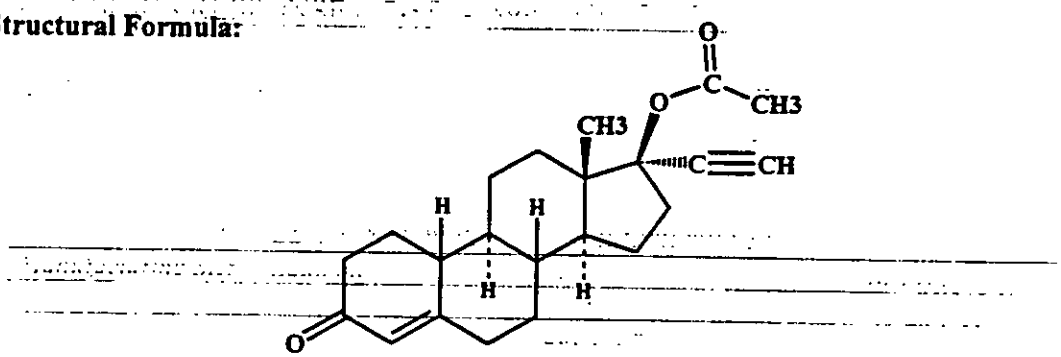
Norethindrone acetate

Chemical Name: [(17-alpha)-17-(acetyloxy)-19-norpregn-4-en-20-yn-3-one]

Molecular Formula: $C_{22}H_{28}O_3$

Molecular Weight: 340.47

Structural Formula:



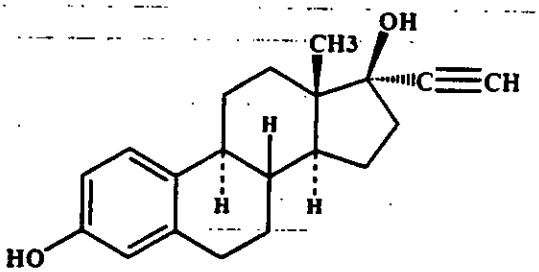
Ethinyl estradiol

Chemical Name: [(17-alpha)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol]

Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.41

Structural Formula:



SUPPORTING DOCUMENTS: NA

RELATED DOCUMENTS (if applicable): NA

NDA 21-065 Sponsor: Parke-Davis Drug: Norethindrone acetate/Ethinyl estradiol

CONSULTS:

Update on Labeling and Nomenclature Committee Tradename Consult:

Due to request and concerns from other ORM Divisions, an e-mail request was sent to the Labeling and Nomenclature Committee on 27-SEP-1999 for the reassessment of the Tradename, FemHRT (See Attachment 3).

The Labeling and Nomenclature Committee responded on 28-SEP-1999 and found the name unacceptable (Also see Attachment 3).

REMARKS:

Amendment Submissions:

Document Date	Submission Contents
24-JUN-1999	Updated stability data for batches of FemHRT Tablets manufactured at the [redacted] to support Expiration Dating.
03-SEP-1999	Updated stability data for batches of FemHRT Tablets manufactured at the Duramed to support Expiration Dating.
17-SEP-1999	Response to IR Letter dated 27-AUG-1999

This review covers the evaluation of responses sent by the sponsor in the information request letter dated 17-SEP-1999 as well as Amendments that followed. The review also contains an evaluation of the stability data for [redacted] and Duramed batches in the determination of expiration dating and related sponsor responses.

The following attachments should be noted:

ATTACHMENT 1: Summary of OOS results from Duramed experimental stability data
ATTACHMENT 2: Calculated data from linear regression analysis of Duramed stability data and comparison of 25°C/60% RH and [redacted] 60% RH data to support equivalence.
ATTACHMENT 3: Labeling and Nomenclature Committee Reassessment of Tradename
ATTACHMENT 4: Establishment Evaluation Review Report

CONCLUSIONS & RECOMMENDATIONS:

From Chemistry Manufacturing and Controls point of view this NDA may be **APPROVED**.

/S/
Michael Ortwerth, Ph.D.
Review Chemist, HFD-580

14-OCT-1999
Date

/S/
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

10/14/99
Date

NDA 21-065 Sponsor: Parke-Davis Drug: Norethindrone acetate/Ethinyl estradiol

cc:
Org. NDA 21-065
HFD-580/Division File
HFD-580/MOrtwerth
HFD-580/DSpellLeSane
HFD-580/MRhee
R/D Init by: MRhee

filename: N21065.002

APPEARS THIS WAY
ON ORIGINAL

SEP 23 1999

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-065 **DATE REVIEWED:** 10-AUG-1999

REVIEW #: 1 **REVIEWER:** Michael Ortwerth

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	16-DEC-1998	17-DEC-1998	23-DEC-1998
AMENDMENT	07-JUN-1999	07-JUN-1999	08-JUN-1999
AMENDMENT	24-JUN-1999	25-JUN-1999	28-JUN-1999
AMENDMENT	20-JUL-1999	21-JUL-1999	26-JUL-1999

NAME & ADDRESS OF APPLICANT:

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106-1047

DRUG PRODUCT NAME

Proprietary: FemHRT
Established: Norethindrone acetate (NA) and Ethinyl estradiol (EE)
Code Name/#: CI-376
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY/INDICATION: Progestin/Estrogen / Hormone Replacement Therapy

DOSAGE FORM: Tablets
STRENGTHS: [redacted] 1 mg NA/5 µg EE [redacted]

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: X Rx __ OTC

SPECIAL PRODUCTS: __ Yes X No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

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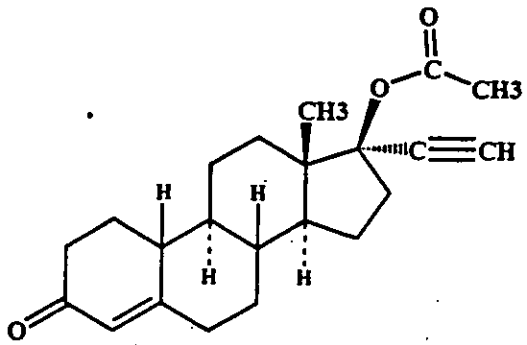

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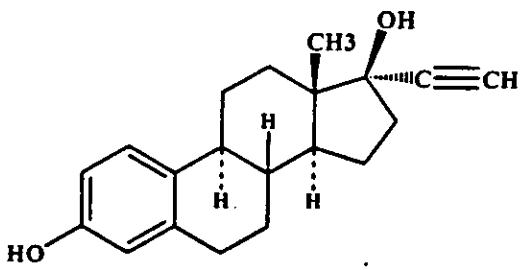

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Manufacturing procedure & quality control of ethinyl estradiol		Adequate	27-FEB-1998 AAl-Hakim	NA
DMF	Manufacturing procedure & quality control of Norethindrone Acetate		Adequate	10-JUN-1998 AMitra	NA
DMF	Packaging Components		Adequate	31-AUG-1999 MOrtwerth	NA
DMF			Adequate	21-SEP-1999 MOrtwerth	NA
DMF			Adequate	29-JUL-1997 CBertha	NA
DMF	Child resistant & Standard threaded closures		Closed[1]	NA	NA
DMF	Canister, 2 in 1 Canister, Canister, Desiccant Packets 2 in 1, Desiccant Packets Desiccant Packets		Adequate	11-MAY-1999 CYaciw	NA
DMF	Rigid PVC Sheet (Marketed as		Adequate	22-FEB-1999 RFrankewich	NA
DMF	Formpack Bottom Foil Printed, Formpack Lidding Foil Unprinted.		Adequate	16-AUG-1999 DKoble	NA
DMF	Push Thru Foil		Adequate	12-SEP-1999 MOrtwerth	NA
DMF	Child resistant & Standard threaded closures		Adequate	26-APR-1999 C-HNiu	NA

[1] This DMF was mistyped as a Type I DMF. It was closed and reopened as a type III DMF #

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

A consult was sent to the Labeling and Nomenclature Committee for trade name, FemHRT and the name were considered acceptable. (See Attachment 1)

REMARKS:

Amendment Submissions:

Document Date	Submission Contents
07-JUN-1999	Letter of Authorization for Resubmitted Type III DMF for Closures.[a]
24-JUN-1999	Updated stability data (24 months) and statistical analysis for batches of FemHRT Tablets manufactured at the facility in
20-JUL-1999	Revision of Content Uniformity specifications.
Anticipated SEP-1999	Updated stability data for batches of FemHRT Tablets manufactured at the Duramed to support Expiration Dating.

[a] Closures originally had a Type I DMF that was determined to be "mis-Typed". The DMF was resubmitted as a Type III DMF

The sponsor requests Expiration Dating for the drug product of 24 months. Currently, a decision on the adequacy of this request is pending the Amendment submission noted above containing updated stability data for the to-be-marketed drug product manufacturer – Duramed.

FemHRT is not currently marketed in any other country. A submission of this NDA is concurrently under review in the

Since the use of the active ingredients for the drug product by the applicant will not exceed the combined total EIC of 1ppb the request for categorical exclusion may be granted.

CONCLUSIONS & RECOMMENDATIONS:

This application is APPROVABLE pending the resolution of chemistry issues stated in the draft deficiency letter.

/S/

Michael Ortwerth, Ph.D.
Review Chemist, HFD-580

22-SEP-1999
Date

/S/

Moo-Jhong Rhee, Ph.D.
ChemistryTeam Leader, HFD-580

9/23/99
Date

cc:
Org. NDA 21-065
HFD-580/Division File
HFD-580/MOrtwerth
HFD-580/DSpellLeSane
HFD-580/MRhee
R/D Init by: MRhee

filename: N21065.001