CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21040

CHEMISTRY REVIEW(S)

Moore

SEP 13 1999

DIVISION OF REPRODUCTIVE AND UROLOGICAL DRUG PRODTCS
HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-040 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 06/30/1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/23/1998	12/29/1998	01/04/1998
Amendment	01/20/1999	01/20/1999	01/22/1999
Amendment	02/11/1999	02/12/1999	02/17/1999
Amendment	04/05/1999	04/06/1999	04/12/1999
Amendment	06/09/1999	06/10/1999	06/18/1999
Amendment	06/24/1999	06/29/1999	07/19/1999

NAME & ADDRESS OF APPLICANT:
The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O.Box 300
Raritan, New Jersey 08869-0602

DRUG PRODUCT NAME

Proprietary:	ORTHO-PREFEST™ Tablets
Nonproprietary/USAN:	17β-Estradiol and Norgestimate
Code Name/#:	RWJ-01551-000 and RWJ-10131-000
Chem.Type/Ther.Class:	4/S

ANDA Suitability Petition/DESI/Patent Status: Not Applicable

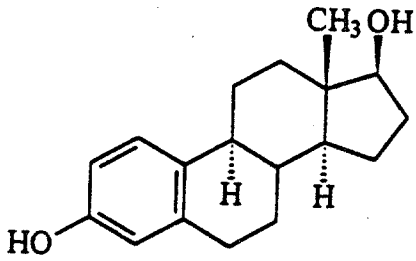
PHARMACOL.CATEGORY/INDICATION:
Hormone Replacement Therapy. Treatment of moderate to severe vasomotor symptoms, vulvovaginal atrophy and prevention of osteoporosis

DOSAGE FORM: Tablets
STRENGTHS: 1mg Estradiol/tablet
1mg Estradiol and 90 μg Norgestimate/tablet

ROUTE OF ADMINISTRATION: Oral
DISPENSED: ✓ Rx ___ OTC

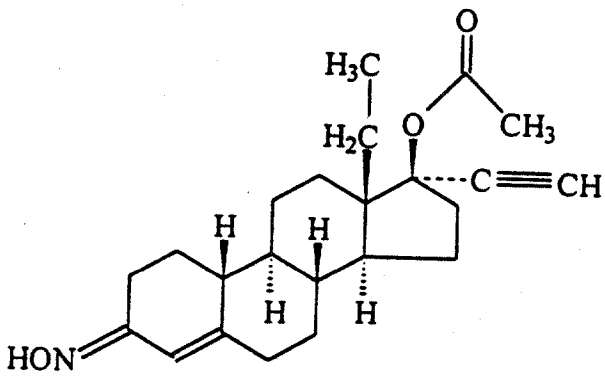
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

- Estra-1,3,5(10)-triene-3,17β-diol.



Molecular Formula: $C_{18}H_{24}O_2$
Molecular weight: 272.39

- (17α)-17-(Acetyloxyl)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-0ne 3-oxime.



Molecular Formula: $C_{23}H_{31}NO_3$
Molecular Weight: 369.50

SUPPORTING DOCUMENTS:

The following is the list of the Drug Master Files related to the application.

DMF / Type	Subject/Item Reviewed	Holder	Status	Review Date and Reviewer Name	Letter Date
DMF	Micronized Estradiol		Adequate	3/18/1998 (D. Lin)	N/A
DMF	Micronized norgestimate		Inadequate	4/19/1999 (A. Al-Hakim)	5/10/99
DMF	DMF		N/A	N/A	N/A
DMF	Rigid PVC film		Adequate	02/13/1999 (R. Frenkewich)	N/A
DMF	Push-thru Blister foil		Adequate	10/15/1998 (B. Berlin)	N/A

RELATED DOCUMENTS (if applicable): None

APPEARS THIS WAY
ON ORIGINAL

CONSULTS: Biopharm.

REMARKS/COMMENTS:

During the reviewing process of the NDA, the applicant has submitted following amendments:

1. Amendment dated 01/20/1999 which contains statement from the firm indicating that only [redacted] will be used as a supplier of norgestimate drug substance
2. Amendment dated 02/11/1999 proposing a new trade name, ORTHO-PREFEST™ replacing the previously submitted IND drug name, PREFEST. The new name has been submitted to the LNC for review (03/04/1999). The committee has approved the new name on 4/28/1999 (copy of the committee's approval form is included in the labeling section of this review).
3. Amendment dated 06/09/1999 that contains a draft color label of the proposed blister card for the finished drug product.
4. Amendment dated 04/05/1999. This amendment contains a revised draft, color label of the proposed blister card as suggested by the division.
5. Amendment dated 06/24/1999. This amendment contains the additional 6 months stability data for the drug product.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from Chemistry, Manufacturing and Control point of view, however, the NDA applicant has to provide additional information delineated in the draft letter.

/S/ 9/10/99
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 9/13/99
Moo Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
Orig. NDA 21-040
HFD-580/Division File
HFD-180/AAl-Hakim
HFD-580/CSO/MooreD/MRhee
R/D Init by: MJ Rhee
AA. Final type 6/30/1999 C:\MSWord\NDA\21040903.1aa

OCT 6 1999

DIVISION OF REPRODUCTIVE AND UROLOGICAL DRUG PRODTCS
HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-040 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 10/06/1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original[1]	12/23/1998	12/29/1998	01/04/1998
Amendment[1]	01/20/1999	01/20/1999	01/22/1999
Amendment[1]	02/11/1999	02/12/1999	02/17/1999
Amendment[1]	04/05/1999	04/06/1999	04/12/1999
Amendment[1]	06/09/1999	06/10/1999	06/18/1999
Amendment[1]	06/24/1999	06/29/1999	07/19/1999
Amendment[2]	10/05/1999	(Fax)	10/05/1999

1. See Chemistry Review No. 1
2. See Chemistry Review No. 2 (this review)

NAME & ADDRESS OF APPLICANT:
The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O.Box 300
Raritan, New Jersey 08869-0602

DRUG PRODUCT NAME

Proprietary: ORTHO-PREFEST™ Tablets
Nonproprietary/USAN: 17β-Estradiol and Norgestimate

Code Name/#: RWJ-01551-000 and RWJ-10131-000
Chem.Type/Ther.Class: 4/S

ANDA Suitability Petition/DESI/Patent Status: Not Applicable

PHARMACOL.CATEGORY/INDICATION:
Hormone Replacement Therapy. Treatment of moderate to severe vasomotor symptoms, vulvovaginal atrophy and prevention of osteoporosis

DOSAGE FORM: Tablets
STRENGTHS: 1mg Estradiol/tablet
1mg Estradiol and 90 µg Norgestimate/tablet

ROUTE OF ADMINISTRATION: Oral
DISPENSED: ✓ Rx _____ OTC

SUPPORTING DOCUMENTS:
The following is the list of the Drug Master Files related to the application.

DMF / Type	Subject/Item Reviewed	Holder	Status	Review Date and Reviewer Name	Letter Date
DMF	Micronized Estradiol		Adequate	3/18/1998 (D. Lin)	N/A
DMF	Micronized norgestimate		Pending	4/19/1999 (A. Al-Hakim)	5/10/99
DMF	DMF		N/A	N/A	N/A
DMF	Rigid PVC film		Adequate	02/13/1999 (R.Frenkewich)	N/A
DMF	Push-thru Blister foil		Adequate	10/15/1998 (B. Berlin)	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:

APPEARS THIS WAY
ON ORIGINAL

Remarks/Comments

- This correspondence (fax received form R.W.Johnson Pharmaceutical research Institute dated 10/06/1999 was submitted in response to our Information Request letter dated 09/22/1999.
- DMF The Holder has not responded yet to our Information Request.
- The EER for site is still pending.

Conclusion & Recommendation:

The R.W.Johnson Pharmaceutical research Institute provided satisfactory responses to our information requests which described in chemistry Review No. 1. However, the application remains Approvable because we have not received a response regarding our information requests from the Drug Master File holder (DMF which manufactured norgestimate drug substance. In addition, site is still pending.

/S/ 10/6/99
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 10/6/99
Moo Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
Orig. NDA 21-040
HFD-580/Division File
HFD-180/AAl-Hakim
HFD-580/CSO/MooreD/MRhee
R/D Init by: MJ Rhee
AA. Final type 10/06/1999 C:\MSWord\NDA\21040903.2aa

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-040 **REVIEW #:** 3 **DATE REVIEWED:** 10/20/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/23/1998	12/29/1998	01/04/1998
AMENDMENT	10/15/1999 (2)	10/18/1999	10/19/1999
	10/20/99	Faxed	10/21/99

NAME & ADDRESS OF APPLICANT:

The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 south
P.O. Box 300
Raritan, New jersey 08869-0602

DRUG PRODUCT NAME

Proprietary: Ortho-Prefest
Established: 17b-estradiol/norgestimate
Code Name/#: RWJ-01551-000 and RWJ-10131-000
Chem.Type/Ther.Class: 4/S

PHARMACOL. CATEGORY/INDICATION:

Hormone Replacement Therapy. Treatment of moderate severe vasomotor symptoms, vulvovaginal atrophy and prevention of osteoporosis

DOSAGE FORM:

Tablets: Three pink tablets containing 17b-estradiol and three white tablets containing estradiol and norgestimate

STRENGTHS:

Pink tablets: 1mg estradiol,
White tablets: 1mg estradiol and 90mcg norgestimate

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

__X__ Rx ___ OTC

SPECIAL PRODUCTS:

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

___ Yes __X__ No

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

Estra-1,3,5(10)-triene-3,17b-diol,
Molecular formula: $C_{18}H_{24}O_2$,
Molecular weight: 272.39

17a)-17-(acetyloxyl)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxime
Molecular Formula: $C_{23}H_{31}NO_3$
Molecular weight: 369.50

REMARKS:

The first amendment dated 10/15/99 is an official submission of earlier faxed document (10/05/99), which was the subject of the Chemistry Rev. #2 (10/06/99).

The second amendment with the same date was submitted in response to the telephone conferences on 09/30/99 and 10/05/99, in which Biopharm issues on dissolution tests, CMC issues on overages of estradiol, expiration date, and a clinical issue on the endometrial biopsy safety reading are discussed.

EER was clarified on 10/19/99 by the Office of Compliance with overall recommendation of "Acceptable".

During a telephone conference on 10/19/99 with Dr. Ramon Polo of RWJ and myself, it was agreed that the format for the established name in the labeling including labels of cartons and immediate containers will be changed from to *(17b-estradiol/norgestimate) tablets.*
This was confirmed by the faxed document on October 20. Also confirmed was the revised Description section; ***"The ORTHO-PREFEST regimen provides for a single oral tablet to be taken once daily. The pink tablet containing 1.0mg estradiol is taken on days one through three of therappy; the white tablet containing 1.0mg estradiol and 0.09mg norgestimate is taken on days four through six of therapy. This pattern is then repeated continuously to produce the constant estrogen/intermittent progestogen regimen of ORTHO-PREFEST."*** , and How Supplied section; ***"ORTHO-PREFEST is available as two separate, round-shaped tablets for oral administration supplied in a blister card with the following configuration; 3 pink tablets followed by 3 white tablets for a total of 30 tablets per blister card."***

The information requests for DMF were all clarified through an amendment dated 09/01/99 to the DMF.

CONCLUSIONS & RECOMMENDATIONS:

The issues on the drug substance, norgestimate, were all clarified through the amendment to the DMF Inspection of the facility for the manufacture of norgestimate was completed satisfactorily. All labeling issues for the "Description" and "How Supplied" sections as well as labels for cartons and immediate container were clarified.

This NDA may now be approved from Chemistry, Manufacturing, and Controls point of view.

/S/ 10/21/99

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-820
@Division of Reproductive and Urologic Drug Products

cc:
Org. NDA 21-040
HFD-580/Division File
HFD-580/MRhee/Dmoore
HFD-180/AAlHakim
R/D Init by: MJRhee
filename: N21040chemrev#3