CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-180

CHEMISTRY REVIEW(S)

NDA 21-180
ORTHO EVRA (norgestimate/ethinyl estradiol) Tablets

3S

R.W. Johnson

PM: Jennifer Mercier
7-4260
HFD-580

Submission Date: August 25, 2000
Goal Date: June 25, 2001

Chemistry Section

NDA 21-180

ORTHO EVRA (norelgestromin/ethynyl estradiol transdermal system)

CHEMISTRY DIVISION DIRECTOR REVIEW

ORTHO EVRA transdermal system is a combination estrogen/progestin contraceptive transdermal patch. The 20 cm^3 patch contains 6.0 mg ethynyl estradiol and 0.75 mg norelgestomin and is designed to deliver 20µg ethynyl estradiol and 150 µg norelgetromin per day.

The ethynyl estradiol **drug substance** is manufactured [redacted] which was found to be acceptable. The manufacturing facility was found to be acceptable from a CGMP perspective. The specifications are USP. The norelgestromin **drug substance** is manufactured [redacted], which was reviewed and was found acceptable. The specifications were improved upon the Division's request The manufacturing facility was found to be acceptable from a CGMP perspective

The **drug product** is a 20 cm^3 patch which delivers 20µg ethynyl estradiol and 150 µg norelgetromin per day. The critical drug release rate testing was established. The patch is comprised of an adhesive matrix in which the drug substances are dispersed along with lauryl lactate which is a penetration enhancer. The primary backing is a polymeric composite and the second is a non-woven polyester mixture. The release liner is a silicone coated polyester film. For critical process operations suitable in-process controls were established. The specifications are considered adequate for quality control and for stability testing. Stability testing supports a 2 year expiry. The product is manufactured by Ortho-McNeil Pharmaceutica, Redwood City CA. The manufacturing facility was found to be acceptable from a CGMP perspective.

Insert, patch and packaging labeling are acceptable. The product trade-name was found acceptable by OPDRA.

Recommendation
From a CMC perspective the application is reccomended for an approval action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Duffy
11/20/01 04:39:42 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-180

ORTHO EVRA

The R.W. Johnson Research Institute

Amit K. Mitra, Ph.D
Division of Reproductive and Urologic Drug Products (HFD-580)

Chemistry Review Data Sheet

1. NDA 21-180

2. REVIEW #:2

3. REVIEW DATE: 11-8-01

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	21-DEC-2000
Amendment	09-FEB-2001
Amendment	14-FEB-2001
Amendment	06-MAR-2001
Amendment	23-MAR-2001
Amendment	27-MAR-2001
Amendment	19-JUL-2001
Amendment	23-AUG-2001
Amendment	27-AUG-2001
Amendment	30-AUG-2001
Amendment	06-SEP-2001
IR letter	27-SEP-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	16-NOV-2001
Amendment	16-NOV-2001
Amendment	14-NOV-2001
Amendment	08-NOV-2001
Amendment	07-NOV-2001
Amendment	07-NOV-2001
Amendment	06-NOV-2001
Amendment	01-NOV-2001
Amendment	24-OCT-2001
Amendment	15-OCT-2001

CHEMISTRY REVIEW

Amendment	12-OCT-2001
Amendment (BL)	05-OCT-2001
Amendment (BC)	05-OCT-2001

7. NAME & ADDRESS OF APPLICANT:

Name:	The R. W. Research Institute
Address:	920 Route 202 South; P.O. Box 300; Raritan, NJ 08869-0602
Representative:	Ramon Polo, Ph.D
Telephone:	908-704-4812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ORTHO EVRA ™
Non-Proprietary Name (USAN): Norelgesrtomin/Ethinyl estradiol Transdermal Drug Delivery System (NRG/EE Transdermal Drug Delivery System)
b) Code Name/: NA
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1, 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: : Combination estrogen/progestin; Prevention of pregnancy.

11. DOSAGE FORM: Transdermal drug delivery system

12. STRENGTH/POTENCY: Norelgestromin/Ethinyl estradiol (6.0 mg/0.75 mg per 20 cm^2) delivering 150 µg norelgestromin, and 20 µg ethinyl estradiol per day

13. ROUTE OF ADMINISTRATION: Transdermal, once a week application

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

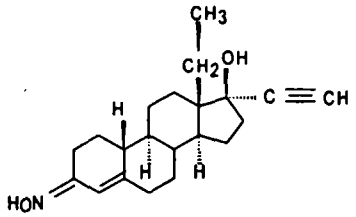
_____SPOTS product – Form Completed

__x__Not a SPOTS product

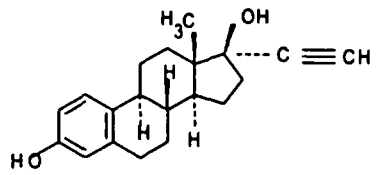
Chemistry Review Data Sheet

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

Norelgestromin - (17α)-17-hydroxy- 13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxime
Ethinyl estradiol - 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)



Norelgestromin



Ethinyl estradiol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	19-OCT-2001	Reviewed by Amit K. Mitra, Ph.D, dated 10-19-01

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type I DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	11-OCT-2001	M. Garcia
Pharm/Tox	None		
Biopharm	Acceptable	16-NOV-2001	Dr. D. J. Chatterjee
LNC	None		
Methods Validation	Will be initiated		
OPDRA	Trademark acceptable	02-APR-2001	C. Holquist
EA	Categorical exclusion granted, EIC less than 1 ppb	NA	NA
Microbiology	Recommends approval	22-OCT-2001	C. Vincent and P. Cooney (see attached E-mail at the end of the review)

Executive Summary Section

The Chemistry Review for NDA 21-180

The Executive Summary

I. Recommendations

A. The NDA 21-180 can be approved with respect to CMC

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, ORTHO EVRA ™, is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestronmin and ethinyl estradiol) in adhesive matrix and a penetration enhancer, lauryl lactate. The transdermal system contains 6.0 mg of norelgestromin and 0.75 mg ethinyl estradiol per 20 Cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day. The 7-day ORTHO EVRA transdermal contraceptive system is the first transdermal contraceptive system to be marketed. It is a flexible 20 cm^2 square with rounded corners.

The ethinyl estradiol is monographed in the USP. The drug substance, norelgestromin is a new molecular entity which exists as a mixture of two geometrical isomers (anti and syn). Based on the manufacturing capability, the acceptance criteria of anti/syn ratio of 1.3 to 1.5 is proposed and deemed acceptable. The sponsor also provided the progestational activities in animal models to show the activity of the two isomers are the same. Both the DMFs for the drug substances (———————) are now adequate to support the NDA after incorporation of certain changes including the tightening of acceptance criteria for related substances.

The drug product is composed of several components. The drug substances are dispersed in an adhesive matrix. It also contains a penetration enhancer (lauryl lactate) and filler (crospovidone). There are two backing in the drug product. The primary backing is a composite consisting primarily of polyethylene. The secondary backing is a non-woven film consisting of two polyesters. A silicone coated polyester film is used as a release liner.

CHEMISTRY REVIEW

Executive Summary Section

The following specification was adopted for the drug product: appearance, identity of drug substances, assay of the drug substances, related substances assay, content uniformity of the drug substances, residual solvents, assay of lauryl lactate (penetration enhancer), release rate of ethinyl estradiol and norelgestromin, release liner peel force, adhesion strength, and microbial limits.

All the test methods and acceptance criteria are deemed satisfactory after the drug product release rate specification was tightened based on data from clinical batches, as recommended by the OCPB reviewer. The release rate specification is now acceptable

The drug product showed significant cold flow when the samples were examined physically. The patch was difficult to remove from the pouch since the backing side sticks to pouch material. This could lead to the change in surface area of the patch (due to folding) and may lead to lack of efficacy. This problem is related to the flow of the adhesive and it occurs as a function of time. To assure that cold flow does not create any problem on shelf life, 2-year-old samples of Ortho Evra were obtained from the sponsor. The samples were distributed among the team members and the conclusion from the panel test was that with proper instruction it is possible to remove the transdermal system without the change in surface area. Since this cold flow problem is related to age of the sample, the sponsor was asked to incorporate the following sentence in the appearance specification: "No changes in surface area should result during removal of the transdermal system from the pouch". The sponsor agreed to incorporate the statement in the appearance specification. The appearance specification is now satisfactory to the reviewer.

The primary stability batches are of the same composition as the formulation that was used in the Phase III clinical studies. Based on two years satisfactory stability data at 25C/60%RH of 3 primary stability lots, an expiration date of 2 years was proposed and it is granted.

B. Description of How the Drug Product is Intended to be Used

ORTHO EVRA designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. Three active patches during first three weeks of a cycle (rotated at different application sites) followed by a 'no-patch' week is the recommended regimen.

The drug product is to be stored under controlled conditions at 25° C; excursions permitted to 15-30 °C (59-86°F).

CHEMISTRY REVIEW

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

There are no pending CMC issues. Therefore, the NDA can be approved with respect to CMC

III. Administrative

A. Reviewer's Signature

Amit K. Mitra, Ph.D

B. Endorsement Block

HFD-580/A. K. Mitra, Ph.D
HFD-580/M.J. Rhee, Ph.D
HFD-580/E.Duffy, Ph.D

C. CC Block

HFD-580/A. K. Mitra, Ph.D
HFD-580/M.J. Rhee, Ph.D
HFD-580/J. Mercier
NDA 21-180

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amit K. Mitra
11/19/01 02:27:13 PM
CHEMIST

David T. Lin
11/19/01 03:03:46 PM
CHEMIST
I concur.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 21-180 **Chemistry Review # 1** **Review Date**: 10-12-01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12-21-00	1-02-01	1-02-01
Amendment	2-09-01	2-12-01	2-12-01
Amendment	2-14-01	2-15-01	2-15-01
Amendment	3-06-01	3-07-01	3-07-01
Amendment	3-23-01	3-26-01	3-26-01
Amendment	3-27-01	3-28-01	3-28-01
Amendment	7-19-01	7-20-01	7-20-01
Amendment	8-23-01	8-24-01	8-24-01
Amendment	8-27-01	8-28-01	8-28-01
Amendment	8-30-01	9-04-01	9-04-01
Amendment	9-6-01	9-10-01	9-10-01

NAME AND ADDRESS OF APPLICANT
The R.W. Johnson Pharmaceutical Research Institute
920 Route
Montville, New Jersey 07450-1000

DRUG PRODUCT NAME
Proprietary: ORTHO EVRA
Non-proprietary/USAN: Norelgesrtomin/Ethinyl estradiol Transdermal Drug Delivery System (NRG/EE Transdermal Drug Delivery System)
Compendium: does not apply
Code name/number: None
Chem. Type/Ther. Class: 1 S, 4S

ANDA SUITABILITY PETITION/DESI/PATENT STATUS: N/A

PHARMACOL. CATEGORY/INDICATION: Combination estrogen/progestin, Prevention of pregnancy.

DOSAGE FORM: Transdermal Drug Delivery System

STRENGTHS: Norelgestromin/Ethinyl estradiol (6.0 mg/0.75 mg per 20 cm^2) delivering 150 ug norelgestromin, and 20 ug ethinyl estradiol per day

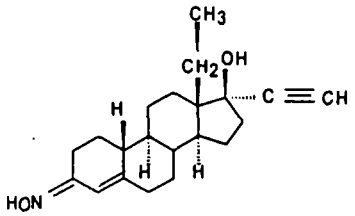
ROUTE OF ADMINISTRATION: Transdermal, once a week application

DISPENSED: By prescription

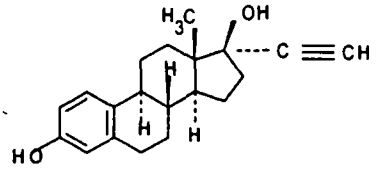
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

Norelgestromin - (17α)-17-hydroxy- 13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxime

Ethinyl estradiol - 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)



Norelgestromin



Ethinyl estradiol

SUPPORTING DOCUMENTS

Type/No.	Subject	Holder	Status	Review Date	Letter Date
II/13025	Norelgestromin	[redacted]	A deficiency letter was sent on 9-25-01	9-17-01	9-25-01
[redacted]				-16-2000	NA
				9-21-1993 (No other amendment on this item has been submitted)	NA
			S. Basaran)	9-26-01	NA

III.	9-26-01	NA
	8-26-99	NA
	9-26-01	NA
	9-23-01	NA

RELATED DOCUMENTS

None

CONSULTS

1. The EER for the manufacturing facilities were submitted. The inspection results are pending
2. The trademark "Ortho Evra" was accepted by OPDRA on 5-1-01.
3. Microbiology was consulted for the microbial limit test and its validation. The review is complete. One Microbiology comment was sent to the sponsor. No response received yet.

REMARKS

1. In the amendment dated 2-14-01, the sponsor provided information about various non compendial excipients/components. Those informations were requested so that the NDA can be filed.
2. In correspondence, dated 2-09-01, [redacted] submitted technical information on the release liner manufactured by the Company.
3. In the amendment dated 3-6-01, the sponsor sent a sample of the transdermal system. The sample was lost during shipping. The sponsor mentioned that the trademark and delivery rates of the actives are heat stamped on the backing.
4. In the amendment, dated 3-23-01, the sponsor of the NDA provided various corrections to the manufacturing facilities. The corrections include change in function of the facility and the street addresses. The corrected facilities were resubmitted for inspection.
5. In the amendment, dated 3-27-01, the sponsor corrected the composition description of the pouch laminate from "A flexible film constructed of [redacted]

6. In the amendment, dated 7-19-01 the sponsor included the following: a. Name change for the manufacturer from [redacted], b. Additional manufacturing site; c. Change in the PIB adhesive acceptance criterion; d. Additional impurities found due to the interaction between the backing laminate with ethinyl estradiol and norelgestromin.

   The additional manufacturing site was included for inspection. The others are reviewed below.

7. In the amendment, dated 8-23-01, the sponsor provided the backing label.
8. In the amendment dated 8-27-01, the sponsor provided the polymorphic form present in the drug substance.
9. In the amendment dated 8-30-01, the sponsor responded to the question whether the clinical responses for the syn and anti isomers of norelgestromin are the same? The sponsor also provided the lot numbers of the norelgestromin used in those clinical lots and their certificate of analysis.
10. In the amendment dated 9-6-01, the sponsor provided the lot #s for the drug product lots manufactured with the release liner from [redacted]

CONCLUSION AND RECOMMENDATION

The application can not be approved until all the deficiencies recorded in the Draft Deficiency letter is satisfactorily answered. An Information Request letter was sent to the sponsor of the NDA on 9-27-01. Satisfactory response to the information requested is necessary for approval of this NDA with respect to CMC.

cc: NDA 21-180
HFD-580/A. K. Mitra, Ph.D
HFD-580/M.J. Rhee, Ph.D
HFD-580/J. Mercier
HFD-820/E. Duffy, Ph.D
R/D. Init. By-

Amit K. Mitra, Ph.D

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW NOTES