

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21-180/S-001**

***Trade Name:*** Ortho Evra

***Generic Name:*** norelgestromin/ethinyl estradiol transdermal system

***Sponsor:*** Ortho-McNeil Pharmaceutical, Inc.

***Approval Date:*** March 04, 2002

***Indications:*** For the prevention of pregnancy.

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*APPLICATION NUMBER:*  
**21-180/S-001**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-180/S-001**

**APPROVAL LETTER**



NDA 21-180/S-001

Johnson & Johnson Pharmaceutical Research & Development  
Attention: Donna Panasewicz  
Senior Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

Please refer to your supplemental new drug application dated January 31, 2002, received February 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO-EVRA™ (norelgestromin/ethinyl estradiol transdermal system).

This "Prior Approval" supplemental new drug application provides for a change in the release rate acceptance criteria at the 24-hour time point.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Moo-Jhong Rhee  
3/4/02 03:54:14 PM

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*APPLICATION NUMBER:*

**21-180/S-001**

**CHEMISTRY REVIEW(S)**

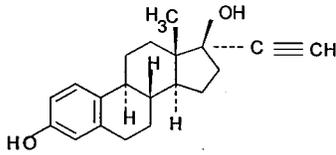
**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG  
PRODUCTS**

**REVIEW OF CHEMISTRY MANUFACTURING AND CONTROLS**

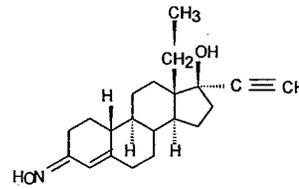
**CHEMIST'S REVIEW #1**

1. NDA NUMBER: 21-180
2. NAME AND ADDRESS OF APPLICANT  
Johnson & Johnson Pharmaceutical Research & Development LLC  
920 Route 202 South  
Raritan, NJ 08869-0602
3. SUPPLEMENT NUMBER/DATE/DATE ASSIGNED  
SCS-001/1-31-02/2-01-02
4. NAME OF THE DRUG: ORTHO EVRA
5. NONPROPRIETARY NAME: Norelgestromin/Ethinyl estradiol Transdermal Drug Delivery System
6. SUPPLEMENT PROVIDES FOR: A change in the release rate acceptance criteria at the 24-hour time point
7. AMENDMENTS/REPORTS/ DATE: None
8. PHARMACOLOGICAL CATEGORY  
Combination estrogen/progestin, prevention of pregnancy.
9. HOW DISPENSED  
Prescription
10. RELATED IND/NDA/DMF/SUPPLEMENT  
None
11. DOSAGE FORM : Transdermal
12. POTENCY  
Norelgestromin/Ethinyl estradiol (6.0 mg/0.75 mg per 20 cm<sup>2</sup>) delivering 150 µg norelgestromin, and 20 µg ethinyl estradiol per day.
13. CHEMICAL NAME AND STRUCTURE

Norelgestromin - (17 $\alpha$ )-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 $\alpha$ )



Ethinyl estradiol  
Molecular wt: 296.40



Norelgestromin  
Molecular weight: 327.47

#### 14. COMMENTS

The acceptance criterion for release rate at 24 hour was proposed to be changed based on the data from the production lots, and extrapolated 24 hours release rate from the clinical lots.

#### 15. CONCLUSIONS AND RECOMMENDATIONS:

The supplement may be approved with respect to CMC. Please issue an approval letter.

Reviewed By: Amit K. Mitra, Ph.D, 2-28-02

R/D INIT. BY: Moo-Jhong Rhee, Ph.D

CC: A. K. MITRA/HFD-580  
M.J.RHEE/HFD-580  
J. Mercier/HFD-580  
NDA 21-180

Redacted   1   page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review

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/s/  
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Amit K. Mitra  
3/1/02 04:15:50 PM  
CHEMIST

Moo-Jhong Rhee  
3/4/02 10:01:54 AM  
CHEMIST  
I concur

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-180/S-001**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology & Biopharmaceutics  
(HFD 860/870/880)  
Tracking/Action Sheet for Formal/Informal Consults

From: **Dhruba J. Chatterjee, Ph.D.**

DATE: 2/22/2002	IND No.: Serial No.:	NDA No. 21-180 Supplement # SCS 001	DATE OF DOCUMENT 1/31/2002
NAME OF DRUG <b>ORTHO EVRA</b>	PRIORITY CONSIDERATION N/A	DATE OF INFORMAL/FORMAL CONSULT N/A	

NAME OF THE SPONSOR: **Johnson & Johnson R&D**

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE**

<input type="checkbox"/> PRE-IND	<input checked="" type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE	<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> ANIMAL to HUMAN SCALING	<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> IN-VITRO METABOLISM	<input type="checkbox"/> IN-VIVO WAIVER REQUEST	<input type="checkbox"/> CORRESPONDENCE
<input type="checkbox"/> PROTOCOL	<input type="checkbox"/> SUPAC RELATED	<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> PHASE II PROTOCOL	<input checked="" type="checkbox"/> CMC RELATED	<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> PHASE III PROTOCOL	<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> ANNUAL REPORTS
<input type="checkbox"/> DOSING REGIMEN CONSULT	<input type="checkbox"/> SCIENTIFIC INVESTIGATIONS	<input type="checkbox"/> FAX SUBMISSION
<input type="checkbox"/> PK/PD- POPPK ISSUES	<input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	<input type="checkbox"/> OTHER (SPECIFY BELOW):
<input type="checkbox"/> PHASE IV RELATED		<i>Prior Approval Supplement</i>

**REVIEW ACTION**

<input type="checkbox"/> NAI (No action indicated)	<input type="checkbox"/> Oral communication with	<input type="checkbox"/> Formal Review/Memo (attached)
<input type="checkbox"/> E-mail comments to:	Name: [ ]	<input type="checkbox"/> See comments below
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox	<input type="checkbox"/> Comments communicated in	<input type="checkbox"/> See submission cover letter
<input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others	meeting/Telecon. see meeting minutes dated:	<input type="checkbox"/> OTHER (SPECIFY BELOW):
(Check as appropriate and attach e-mail)	[ ]	[ ]

**REVIEW COMMENT(S)**

**NEED TO BE COMMUNICATED TO THE SPONSOR**       **HAVE BEEN COMMUNICATED TO THE SPONSOR**

**COMMENTS**

ORTHO EVRA was approved by the Agency in Nov, 2001. The *interim* dissolution specifications for this transdermal product were set (based on the available data on the clinical trial formulations) at 0.5 hr, 2 hr, 8hr and 24 hr time points (the 24 hour time point was added by the Agency). Please refer to original CPB review on NDA 21-180 for our proposed dissolution specifications.

In this prior-approval supplement, additional data was sent in by the sponsor on dissolution (individual data on all the / production batches). The sponsor is currently proposing that the 24-hour specification be changed to > / % for NGMN and > / % for EE. The following were the statistics computed from the data submitted on the 24 hour time point (for all / production batches)

	EE	NGMN
% Formula Strength (FS)		
Dissolved @ 24 hr.		
Mean	73.9	71.4
SD	4.5	3.5
Minimum	[ ]	[ ]
Maximum	[ ]	[ ]

The proposed change (as mentioned above) is acceptable to OCPB. The following went into consideration while arriving at this decision:

- 1) In absence of IVIVC, a ± / % (FS dissolved) was allowed on the overall means at different time points. Therefore, at the 24 hr time point the specifications are, not less than [ ] % (for EE) and [ ] % (for NGMN).

- 2) Review of the data initially submitted to the NDA indicated that it takes  $\approx 96$  hours for  $> \text{ } \%$  dissolution of NGMN and EE
- 3) A modeling analysis in which the sponsor projected the 24 hour dissolution profile of the *phase 3 clinical batches* (note: 24 hr. dissolution data for the clinical batches were not determined since it was not in the original specifications) show that around  $\text{ } \%$  FS dissolved was the lowest value (among the 3 clinical batches) at 24 hr for NGMN and EE, and this provides additional justification for approving specifications at 24 hours no less than  $\text{ } \%$  for either.

The above was discussed with Dr. Malinowski (Director, DPE 2 on 2/20/02), Dr. Parekh (TL), and in a meeting with the CMC team and Jen Mercier (PM) on 2/22/02.

Based on the analysis of complete data submitted by the sponsor post-approval, the following should be the dissolution specifications for ORTHO EVRA:

% FS for NGMN				% FS for EE			
0.5 hr	2.0 hr	8.0 hr	24 hr	0.5 hr	2.0 hr	8.0 hr	24 hr
$\text{ } \%$	$\text{ } \%$	$\text{ } \%$	$> \text{ } \%$	$\text{ } \%$	$\text{ } \%$	$\text{ } \%$	$> \text{ } \%$

**Comments to the Sponsor:**

The sponsor is hereby reminded again to submit data justifying choice of the current dissolution medium (eg. how would the dissolution profile/results appear using conventional aqueous media, or that containing a  $\text{ } \%$ , or containing lower concentrations of  $\text{ } \%$ ).

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/s/  
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Dhruba Chatterjee  
2/25/02 02:55:16 PM  
BIOPHARMACEUTICS  
Cuurent diss. spec. proposal acceptable

Ameeta Parekh  
2/25/02 04:09:02 PM  
BIOPHARMACEUTICS  
I concur

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*APPLICATION NUMBER:*  
**21-180/S-001**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-180

**PRIOR APPROVAL SUPPLEMENT**

Johnson & Johnson Pharmaceutical Research & Development  
Attention: Donna Panasewicz  
Senior Director, Regulatory Affairs  
920 P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO EVRA<sup>TM</sup> (norgestromin/ethinyl estradiol) Transdermal Patch.

You were notified in our letter dated February 14, 2002 that your supplemental application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your supplemental application has been accepted as of February 14, 2002.

Unless we notify you within 60 days of the above 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 April 14, 2002 in accordance with 21 CFR 314.101(a).

If the application is filed, the primary user fee goal date will be August 14, 2002

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 Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products  
Attention: Division Document Room, 17B-20  
5600 Fishers Lane  
Rockville, Maryland 20857

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

Sincerely,

Terri Rumble, B.S.N.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug  
Products; HFD-580  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Jeanine Best  
2/14/02 02:10:23 PM  
Signing for Terri Rumble



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-180/S-001

Johnson & Johnson Pharmaceutical Research & Development  
Attention: Donna Panasewicz  
Senior Director, Regulatory Affairs  
920 P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ORTHO EVRA™ (noregestromin/ethinyl estradiol) Tansdermal Patch  
NDA Number: 21-180  
Supplement number: S-001  
Date of Application: January 31, 2002  
Date of receipt: February 1, 2002

We note that you are in arrears for payment of fees for products, or establishments, or previously submitted applications.

Because an application is considered incomplete and cannot be accepted for filing until all fees owed have been paid, review of the application referenced above may not begin at this time. Upon receipt of the outstanding fees, we will start the user fee clock and commence review of your application. Payment should be submitted to the following address:

Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)  
Mellon Client Service Center, Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

**NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.**

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplement should be addressed as follows:

U.S. Postal Service: Courier/Overnight Mail:  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Attention: Division Document Room, 17B-20  
5600 Fishers Lane  
Rockville, Maryland 20857

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

Sincerely,

Terri Rumble, B.S.N.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Jeanine Best  
2/14/02 11:50:46 AM  
Signing for Terri Rumble



NDA 21-180

**PRIOR APPROVAL SUPPLEMENT**

Johnson & Johnson Pharmaceutical Research & Development  
Attention: Donna Panasewicz  
Senior Director, Regulatory Affairs  
920 P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ORTHO EVRA™ (norgestromin/ethinyl estradiol) Tansdermal Patch  
NDA Number: 21-180  
Supplement number: s-001  
Date of supplement: January 31, 2002  
Date of receipt: February 1, 2002

Unless we notify you within 60 days of the 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 April 1, 2002 in accordance with 21 CFR 314.101(a).

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Division of Reproductive and Urologic Drug Products, HFD-580  
Attention: Division Document Room, 17B20  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA-21-180/S-001

Page 2

If you have any question contact me at (301) 827-4260.

Sincerely,

Jennifer Mercier  
Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Jennifer L. Mercier  
2/5/02 12:09:36 PM