Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

09 OCT 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

BM
NDA ORIG AMENDMENT

2001 HFD-580 EVALUATION AND RESEARCH

Amendment to a Pending Application:
Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to Ms. Mercier's 09 August 2001 telephone call to request information. The request was for additional information on 2 subjects as follows:

- For study CONT-003, Subject No. 1181, the hospital discharge summary is requested.
- For study CONT-002, Subject No. 21022, the operative note and two hospital discharge summaries are requested.

At this time we wish to provide a letter of our efforts to obtain this information as requested by the Medical Reviewer. This information is provided in the attached letter.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

NAI - 10/13/01
/S/

Ramon Polo, PhD
Director
Regulatory Affairs

Desk copy to: Dr. Daniel Davis,
Medical Reviewer, DRUDP

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

N:\[redacted]LTR\100801.doc/08 October 2001/JU

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

05 OCT 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Chemistry, Manufacturing and Controls (CM&C)

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to an NDA amendment dated 19 July 2001 which included the addition of the —— .....a facility in the manufacturing process. At this time, we wish to amend the NDA and delete this facility from the application. An explanation of this change is provided behind the tab titled "Manufacturing Address". In addition, section 3.4 of the NDA has been amended to delete the —— facility and a copy is provided with this submission. We hope that this minor amendment will be reviewed without effecting the action date.

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to the FDA district office in North Brunswick, New Jersey as well as the Redwood City FDA district office in Alameda, California. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD 20857
Phone No: (301) 827-4260

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
The R.W. Johnson Pharmaceutical Research Institute	05 OCT 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(908) 704-4812	(908) 203-1499

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 21-180**

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
norelgestromin and ethinyl estradiol	ORTHO EVRA™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
transdermal patch	6 mg norelgestromin 0.75 mg ethinyl estradiol	Transdermal

(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples 21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent Information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Ramon Polo, PhD **Director, Regulatory Affairs**	**05 OCT 2001**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 **Raritan, New Jersey 08869-0602**	**(908) 704-4812**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Manufacturing Address

Please delete all references to the _____. Because of delays in acquiring and validating the new equipment, the laboratory and site are not ready for use at this time for the activities listed in 1.

APPEARS THIS WAY
ON ORIGINAL

3.4. Manufacturer

3.4.1. NAME AND ADDRESS

EVRA ™ Transdermal Contraceptive system is manufactured at the following facility:

Ortho-McNeil Pharmaceutical, Inc.
Drug Delivery System Division (OMP-DDD)
701 Galveston Drive
Redwood City, CA 94063

The specific activities conducted at this facility are:

All manufacturing, testing, labeling, and related control operations are conducted in accordance with the provisions of current Good Manufacturing Practices as promulgated in 21 CFR.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

05 OCT 2001

Susan Allen, MD, Director
Division of Reproductive and Urologic
Drug Products HFD-580

Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

N000 (BL)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Dr. Allen:

NDA ORIG AMENDMENT

Reference is made to our pending NDA 21-180 for ORTHO EVRA™ and to the draft package components submitted with the original application on 20 December 2000 NDA (Item 2, Item Volume 1, Pages 52-59). We are amending NDA 21-180 at this time with copies of the proposed packaging components for the finished drug product as follows:

Black and white copies of:
•The pouch overwrap to be applied to blank pouches (quantity 2)
•The draft pouch text (quantity 3)
• Instructions for Use - To be provided in addition to the Physician and Patient Label (quantity 3)

Color copies of:
•Carton -Trade (quantity 1)
•Carton - Clinic (quantity 1)
•Carton - Sample (quantity 1)
•Packer Tray - Trade (quantity 1)
•Packer Tray - Clinic (quantity 1)
•Packer Tray - Sample (quantity 1)
•Patch Change Reminder Stickers (quantity 3)
•Sample labels to be applied to the cosmetic bag containers post-launch (quantity 3)

This amendment is being provided at this time in order to gain a preliminary review of the text and text formatting planned. In some instances, only one copy of the draft component is enclosed, as this is all that we have available at this time.

Please note that these components were prepared prior to receiving the CMC Reviewer's September 27 request to add two additional inactive ingredients to the pouch and carton labels. We will try to add "polyester backing film laminate" and

"polyester release liner" as requested. There is little space however, available for additional text and we do not want to jeopardize the readability of the pouch text.

In addition, the trade and clinic cartons and packer trays as well as the sample labels for the cosmetic bag containers contain an error in the placement of the closed parenthesis. The parenthesis should appear in all cases after the word "system", not after the word "estradiol". This error will be corrected immediately.

If you have questions regarding this information please contact me at (908)-704-4812 or Valerie Donnelly at (908)-704-5891 or our dedicated number for FDA use (908)-704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo Ph.D.
Director
Regulatory Affairs

Enclosures

APPEARS THIS WAY
ON ORIGINAL

N:\norgesti\ltr\labelupdate

REVIEWS COMPLETED

CSO ACTION

LETTER N.A.I. MEMO

CSO INITIALS DATE

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

01 OCT 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

N000(BM)

NDA ORIG AMENDMENT

Amendment to a Pending Application:
Full Study Reports

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to the abbreviated study reports contained in the NDA for studies, NRGEEP-PHI-017 and NRGEEP-PHI-018. The abbreviated reports are contained in NDA Item 8/Item Volumes 7 and 8, respectively). At this time, we would like to provide the full study reports for your information and review. This submission is comprised of three volumes. The study report for NRGEEP-PHI-017 is contained in Volumes 1 and 2; the study report for NRGEEP-PHI-018 is contained in Volume 3. We apologize for the delay in this submission and hope that it will not extend the review clock.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

Desk copy to: Dr. Daniel Davis,
Medical Reviewer, DRUDP

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

27 SEP 2001

BC

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180 NDA ORIG AMENDMENT
ORTHO EVRA™

Amendment to a Pending Application
Response to Request for CMC Samples

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. At this time we wish to provide additional CM&C information as requested by the CMC Reviewer.

Chemistry, Manufacturing and Controls Information:

Enclosed are 19 samples of the heat-stamped ORTHO EVRA™ transdermal contraceptive system. These patches should mimic what we propose to release in the marketplace. Please note that these patches contain active ingredients and should be handled accordingly. For the purposes of this submission, the systems are sealed in a plastic protector.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

cc: Desk copy to Dr. Amit Mitra, CM&C Reviewer HFD-580

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

N225C

NDA ORIG AMENDMENT

06 SEP 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to Dr. Amit Mitra's 29 August 2001 voice mail request for information. The information is provided with the FDA question stated in **boldface** type followed by RWJPRI's respsonse.

Was the [redacted] supplied by [redacted], used in clinical or tox studies?

[redacted] supplied by [redacted], was used in batch number 01607. Batch No. 01607 was not used in toxicology studies but was used in the clinical studies listed below in Table 1.

Table 1. Batch No. 01607/ [redacted]

Human Pharmacokinetic Studies	Clinical Safety and/or Efficacy Studies
NRGEEP-PHI-012	NRGEEP-PHI-007
NRGEEP-PHI-013	NRGEEP-PHI-008
NRGEEP-PHI-014	NRGEEP-PHI-009
NRGEEP-PHI-015	NRGEEP-PHI-011
NRGEEP-PHI-016	
NRGEEP-PHI-017	

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEM

N:\[redacted]LTR\090501 cmc amend.doc/05 September 2001/JU

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to our FDA district offices in North Brunswick, New Jersey and Oakland, California. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director, Regulatory Affairs

Send 1 desk copy to:
Dr. Amit Mitra
Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD
Ph: (301) 827-4238

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

30 AUG 2001

BC

NDA ORIG AMENDMENT

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to Ms. Mercier's 24 August 2001 email request for information. At this time we wish to provide this information, as requested by the Reviewing Chemist. In addition, we are providing impurities on a fourth lot (no. S-97-0306-A) for question number 3, as requested in a 27 August 2001 telephone conversation with Dr. Amit Mitra. This letter is formatted with the FDA question stated in **boldface** type followed by RWJPRI's respsonse.

Question 1:
Are the clinical responses the same for anti and syn isomers of 17-deacetylnorgestimate?

The anti and syn isomers are equi-active based on pharmacological studies including progestogen receptor binding, endometrial proliferation assay in rabbits and antiovulatory and antiestrogenic assays in rats. This is the conclusion of pharmacology study, Progestational Activities of anti-(RWJ-407395) and syn-(RWJ-407396) Isomers of Norelgestromin (17-Deacetylnorgestimate)", EDMS-USRA-6063655:2.0". This study report is submitted for your information following the tab titled, "Study Report, EDMS-USRA-6063655:2.0".

Question 2:
Lot #s of the pivotal clinical trial lots of the drug product: lot # of deacetylnorgestimate used in those clinical lots, and their certificate of analyses containing anti / syn ratios of deacetylnorgestimate

Response:
The pivotal clinical trial lots of drug product and the lot number of the deacetylnorgestimate used in those clinical lot are as follows:

Pivotal Clinical Trial Lot Number of Drug Product	Lot Number of Drug Substance
01107	J740480
01517	J740490
01607	J750500

The Certificates of Analysis, which contain the anti / syn ratios of deacetylnorgestimate for these three lots, follow behind the tab titled, "Certificates of Analysis".

Question 3:

Total impurities for 17-deacetylnorgestimate lot numbers (J&J) –S-97-0106-A, S-97-0107-A, S-97-0105-A and S-97-0306-A during the stability study.

Response:
Additional stability data for the first three lots have been generated at the 36 and 48 month stability time points. Additional stability data for the fourth lot has been generated at the 24 and 36 month time points. The impurity data for the four lots of 17-deacetylnorgestimate are:

PRI Drug Substance Stability Study Number	Substance Lot Number	Age of Sample, Months	Total Impurities
S-97-0106-A	J740490	36	
S-97-0106-A	J740490	48	
S-97-0107-A	J740500	36	
S-97-0107-A	J740500	48	
S-97-0105-A	J740480	36	
S-97-0105-A	J740480	48	
S-97-0306-A	R5C0200	24	
S-97-0306-A	R5C0200	36	

The corresponding manufacturer's lot number is also included for completeness.

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to our FDA district office in North Brunswick, New Jersey. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Valerie A Donnelly for /

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to:
Dr. Amit Mitra
Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD
Ph: (301) 827-4238

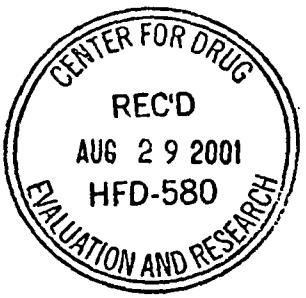
APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NDA ORIG AMENDMENT NJ-FSM 28 AUG 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

Amendment to a Pending Application:
Response to Request for Additional Clinical Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to Ms. Mercier's 15 August 2001 email request to provide additional information and clarification. At this time we would like to amend the NDA to include the following clinical information. FDA's request appears in **bold-face** type followed by RWJPRI's response.

A list of all pregnant women (pre, on-Rx, post); include patient identification numbers.
This information is provided for ease of review behind the tab titled, "Pregnancy Data Listing". It may also be found in the original application, as Pregnancy Data listing, Attachment 6.2 in Item 8/Item Volume 23/Pages 177-179.

Identify the NDA location where the pregnancy reporting form and data for each pregnant woman (volume # or CD-ROM) can be found.
As noted in the Overall NDA Reviewer's Guide included in Item 1 of the original application, this information was provided on CD-ROM as part of Item 12, Case Record Forms. The actual CD-ROM was located in the Archival copy of the first volume of the NDA (NDA Volume 1.001). A copy was also provided with Item 11 in the Clinical/Statistical Reviewer's Jacket in the original application.

A copy of Item 12 on CD-ROM is included with this submission for ease of review. The index contained on the CD-ROM identifies the subjects who became pregnant. A copy of pages 175-177 of this index is also provided here for ease of review behind

the tab titled, "Pregnancy Reporting Form Index", as these pages identify the pregnant subjects by number, investigator and treatment.

In addition, as discussed at the Pre-NDA meeting on 27 July, 1999, RWJPRI proposed to submit ultrasound reports for some of the pregnant subjects, since the reports enhanced information that was provided on the CRFs. These reports are also provided on the CD-ROM.

All CD-ROMs have been scanned and deemed virus-free using McAfee Vshield w/SP, program version 4.5.0.534, scan engine version 4.1.40, virus definition 4.0.4154.

Number of women age 18-35 and number of women age 36-45 per study, 002, 003, and 004.
This data is provided in tabular format behind the tab titled, "Number of Women by Age".

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Valerie A Donnelly for/

Ramon Polo, PhD
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

9/5/01 - NDA review pending /S/

REVIEWS COMPLETED

CS[illegible] MEMO

CSO INITIALS DATE

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

INDA ORIG AMENDMENT N-180

27 AUG 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Response to Request for Chemistry, Manufacturing and Controls (CM&C) Clarification

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to Dr. Mitra's 22 August 2001 telephone request that we identify the exact polymorphic form that the drug substance, norelgestromin (NGMN), exists in. At this time we wish to provide the information requested. This letter is formatted with the FDA question stated in bold face type followed by RWJPRI's respsonse.

The Physical-Chemical Characterization Report in the NDA reported 3 polymorphic forms of the drug substance, NGMN, one amorphous and two crystalline. Please identify what form the drug exists in. If it is in crystalline form, please identify which of the two it exists in.

As described in "Physical-Chemical Characteristics," Section 2.1.1.3 of NDA 21-180, Item 4/Item Volume 1/ Pages 5-6,

> *The polymorph screen of 17-deacetylnorgestimate yielded seven forms. The thermogravimetric data show that forms B, C, D, and F may be hydrated/solvated forms, whereas forms A, E and G did not contain significant volatiles. The intraconversion studies of the unsolvated forms show that Form E is the most stable form of 17-deacetylnorgestimate at room temperature.*

Therefore, the crystalline form of norelgestromin used is Form E, as it has been determined to be the most stable polymorph of norelgestromin.

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to our FDA district office in North Brunswick, New Jersey. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Valerie A. Donnelly for/

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to:
Dr. Amit Mitra
Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD
Ph: (301) 827-4238

APPEARS THIS WAY ON ORIGINAL

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

DESK COPY

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

23 AUG 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. We are providing information at this time as per your 15 August 2001 request. Included are the following:

Additional desk copies of information already provided in the original application:
Item 3/Volume 1.003:

- Chapter 1, Proposed Text of the Labeling for ORTHO EVRA™ - Annotated
- Chapter 2, Pharmacologic Class, Scientific Rationale, Intended Use and Potential Benefits
- Chapter 8, Integrated Summary of Benefits and Risks.

Item 8/Volumes 1.090 -1.093:

- Integrated Summary of Efficacy
- Integrated Summary of Safety.

Samples of imprinted backing label:
Enclosed behind the tab titled, "3 sample patches", please find three samples of ORTHO EVRA™ transdermal systems with the trademark and delivered dose imprinted as a heat-stamp on the backing. These patches contain active ingredients and should be handled accordingly. Sample patches were previously requested by the CMC Reviewer and submitted to the agency, with a CM&C, NDA amendment, on 14 February 2001. The samples however, were inadvertently omitted from the submission and therefore a second amendment was filed on March 6 2001. The 6 March 2001 submission included three active samples.

Item 2, Draft Packaging Components:
In addition, as per a telephone discussion with Dr. Amit Mitra on 22 August, we would like to amend NDA Item 2, Draft Packaging Components, to include a color copy mock-up of the proposed heat-stamp on the patch. This mock-up includes the name of the drug product (ORTHO EVRA) and the delivered dose (150/20), as previously requested by the Agency and may be found behind the tab titled, "Packaging Components".

As a separate submission, we will also provide as per your request:

- A list of all pregnant women (pre, on-Rx, post) with patient identification numbers.
- The NDA location of the Pregnancy Reporting Form and data for each of the pregnant women (Item Volume No./Volume No./Page No.)
- [redacted]

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

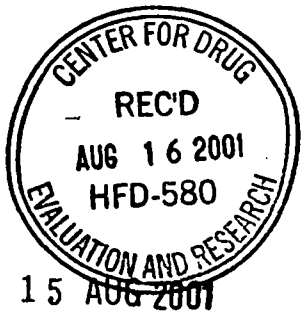
The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Desk Copy w/enclosures: Send to Jennifer Mercier at FDA, DRUDP

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL



15 AUG 2001

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System
ORIG AMENDMENT
BM

Amendment to a Pending Application:
Clinical (Case Report Forms)

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to the Medical Reviewer's request on 13 August 2001 to provide Case Record Forms (CRFs) for Subject No. 21022, who participated in study NRGEEP-CONT-002. At this time we would like to amend the NDA to include these CRFs. The CRFs for this subject were not included in Item 12 of the original NDA, as this subject did not meet the criteria for inclusion (death or discontinuation due to an adverse event). The CRFs were however, included in a submission to [redacted] Serial No. 088 on 28 April 2000. We are providing a paper copy of the CRFs and additional miscellaneous records with this submission as well as an electronic PDF version on CD-ROM. All CD-ROMs have been scanned and deemed virus-free using McAfee Vshield program version 4.5.0.534, scan engine version 4.1.40, virus definition 4.0.4153.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

NDA review pending

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk copy to: Jennifer Mercier, DRUDP, HFD 580

N:[redacted]LTR\081501 req CRFs.doc/14 August 2001/JU

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

19 JUL 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Chemistry, Manufacturing and Controls (CM&C)

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to the two-page summary of changes faxed to the Agency on 10 July 2001. At this time we wish to provide the details of the updated CMC information in an effort to have it reviewed without effecting the action date. This submission includes the functions of both of the California facilities, as requested by the CMC Reviewer on 17 July 2001.

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to the FDA district office in North Brunswick, New Jersey as well as the FDA district office in Oakland, California. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Valerie A Worsey for /

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD 20857
Phone No: (301) 827-4260

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

12 JUN 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

NDA ORIG AMENDMENT

Amendment to a Pending Application:
Clinical (Financial Disclosure)

N 000 BM

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to Ms. Jeanine Best's request on 18 May 2001 to provide additional Financial Disclosure Information. At this time we would like to amend the NDA to include a revised Financial Disclosure Classification Table. The revised table contains a new column as requested, for "Number of Subjects Enrolled" at each of the Principal Investigators sites. We hope that you will find this information acceptable.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

Desk copies to:
Jeanine Best, DRUDP, HFD 580
Jennifer Mercier, DRUDP, HFD 580

N [redacted]ALTR\061101 NDA clinical amend .doc/07 June 2001/JU

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NDA ORIG AMENDMENT

0 8 MAY

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Labeling

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. At this time, as required by oral contraceptives class labeling, we wish to provide the Patient Package Insert, Brief Summary. This document was prepared using text from the Labeling Guidance for Combination Oral Contraceptives Document and text from the Patient Package Insert - Detailed Information for the Patient that was included in the original application.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

N [redacted]\LTR\nda amend-pt brief instruct.doc/04 May 2001/JU

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

ORIG AMENDMENT
SU

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic
Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norgelgestromin/ethinyl estradiol
transdermal system)

NDA ITEM 9:
Four-Month Safety Update

/S/ 4-23-01

Dear Dr. Allen:

Reference is made to pending NDA 21-180 for ORTHO EVRA™ submitted on 21 December 2000, for the prevention of pregnancy. As per 21 CFR 314.50(5)(d)(vi)(b) we are required to submit the Four-Month Safety Update.

Current ongoing studies include two Phase 1 bioequivalence protocols, NRGEEP-PHI-021 and NRGEEP-PHI-022. An additional Phase 1 bioequivalence protocol, NRGEEP-PHI-020, has completed enrollment and sample analyses are in progress. With the exception of the Narrative provided for one subject in protocol NRGEEP-PHI-022 [redacted] there are no additional safety adverse event data to report from these studies at this time. With the exception of these three bioequivalence studies, all clinical safety and adverse event data from the ORTHO EVRA™ program were included in the NDA. At this time we wish to provide additional safety information. The information is comprised of:

•One Pregnancy Narrative and Case Report Form from an ongoing Phase I study, NRGEEP-PHI-022
•Fifteen (15) Narrative Summaries for Pregnancies and Infant Outcome Reports that occurred in the completed ORTHO EVRA™ Phase III studies, NRGEEP-CONT-002, NRGEEP-CONT-003 and NRGEEP-CONT-004.

A database search was performed by the [redacted] post-NDA submission. This search covered the reporting period of 21 December 2000 through 31 March 2001. No new serious adverse event, pregnancy or follow-up information was reported.

[redacted]

If you have questions about this submission, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

4/20/01
Will be part of my NDA review -
I have a desk copy
/S/

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

ORIG AMENDMENT 27 MAR 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™

RC

Amendment to a Pending Application
Chemistry, Manufacturing & Controls Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. At this time we wish to provide an update to the paper/foil pouch stock material, specification 1005.

Chemistry, Manufacturing and Controls Information
The pouch material utilized in the phase III clinical studies remains the same. Specification 1005 has been revised to include the correct pouch description as outlined below:

FROM: [redacted]

TO: [redacted]

Attached is a copy of the updated specification.

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to the FDA district office in North Brunswick, New Jersey and San Francisco, California. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ FAX ☐ MEMO

\\RARUSRARES01\PRIUSREG\[redacted]\LTR\SPECIFICATION 1005 UPDATE.DOCspecification 1005 update

We apologize for any confusion that this may have caused. Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

ORIGINAL

23 MAR 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Chemistry, Manufacturing and Controls (CM&C)

ORIG AMENDMENT

Dear Dr. Allen:

BC

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. At this time we wish to provide revised CMC information to more accurately reflect the facilities involved with the drug substances and drug product. The changes are outlined below and copies of the two tables are attached.

CMC Table 1: Facilities Involved in Testing and Warehousing of Active Drug Substances:

- Ortho-McNeil Pharmaceutical, Inc.: added the responsibility, "sampling of active drug substance".

3. Changed the responsibility of this facility from "storage and sampling of excipients" to "warehousing of bulk patches".

- [redacted]
- [redacted]
- [redacted] itical

Field Copy Certification: In accordance with 21 CFR 314.50(k)(3), a field copy containing the Chemistry Manufacturing and Controls Information contained in this amendment has been provided to our FDA district office in North Brunswick, New Jersey. We certify that the field copy submitted is a true and accurate copy of the archival and review copies of this amendment.

We apologize for any confusion that this may create. Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Valerie A Donnelly for /

Ramon Polo, PhD
Director
Regulatory Affairs

APPEARS THIS WA.
ON ORIGINAL

Fax 1 desk copy to:
Dr. Amit Mitra
Reviewing Chemist
FDA/DRUDP
HFD-580
Rockville, MD

Fax No: (301) 827-4267

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

06 MAR 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™

Amendment to a Pending Application
Chemistry, Manufacturing & Controls Information

ORIG AMENDMENT
BC

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. At this time we wish to provide additional CM&C information as requested by the CMC Reviewer.

Chemistry, Manufacturing and Controls Information

The backing label with the trademark and delivery rate imprinted on it. These sample patches were inadvertently omitted from the 14 February 2001 CM&C submission. Please note that the samples enclosed (a total of three) contain active ingredients and should be handled accordingly. We apologize for any confusion that this may have caused.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

ORIGINAL

09 FEB 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
NEW CORRESP
1/C

Other:
Response to FDA Request For Information, Additional Desk Copies

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. At this time we wish to provide, as per your request, additional desk copies of information already provided in the original application. We are providing the following:

- Three copies of the CM&C, Methods Validation Package (NDA, Item 4C Volumes 6 & 7)
- One paper copy of NDA Overall Volume 1.001
- Two paper copies of NDA Overall Volume 1.002
- One CD-ROM which contains the unannotated labeling (Item 2)

The CD-ROM has been scanned and deemed virus-free using McAfee VShield program version 4.5.0.534, scan engine version 4.1.20, virus definition 4.0.4119. Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED
CSO
☐ L☐ ☒ N.A.I. ☐ MEI
CSO INITIALS DATE 2/10/01

Desk Copies: Send to Jennifer Mercier at FDA, DRUDP

N[redacted]\LTR\response to fda req copies 020901 doc/08 February 2001/JU

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

JAN 0 5 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

NEW CORRESP

NC

Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to the Agency's 02 January 2001 request to provide two additional desk copies of NDA Volume 1. Two desk copies are provided in this submission. Each copy also contains one copy of the CD-ROM that was provided in the original Volume 1.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Valerie A Donnelly for /

Ramon Polo, PhD
Director
Regulatory Affairs

Send Desk Copies to the attention of Ms. Jennifer Mercier

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

DEC 2 1 2000

Dr. Susan Allen, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II, (HFD-580)
Division of Reproductive and Urologic Drug Products
Att.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180/User Fee 3894
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

NEW DRUG APPLICATION

Dear Dr. Allen:

Pursuant to the provisions of section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, The RW Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a New Drug Application for ORTHO EVRA™ (norelgestromin/ethinyl estradiol) transdermal system. ORTHO EVRA™ is indicated for the prevention of pregnancy. The following numbers were assigned to this application: NDA 21-180 and User Fee No. 3894. This application was prepared in accordance with 21 CFR 314. 50 and applicable guidelines.

ORTHO EVRA™ consists of the norelgestromin (NGMN) as the progestin and ethinyl estradiol (EE) as the estrogen. ORTHO EVRA™ will be provided in a pouch containing one beige transdermal system. ORTHO EVRA™ is a combination transdermal contraceptive patch with a contact surface area of 20 cm^2. It contains 6.0 mg of NGMN and 0.75 mg EE, and releases 150 micrograms of NGMN and 20 micrograms of EE per 24 hours. A single patch will be applied once a week for three consecutive weeks followed by one patch-free week.

Naming Conventions

The United States Adopted Names Council (USAN) and the International Non-Proprietary Name Committee (INN) of the World Health Organization (WHO) adopted norelgestromin, as the generic name for 17-deacetylnorgestimate. The full generic name for our transdermal system is therefore, norelgestromin/ethinyl estradiol. For purposes of this NDA, we are providing this explanation here and in each of the Reviewers Guides, noting that the active ingredients 17-deacetylnorgestimate and ethinyl estradiol (17d-NGM/EE) were used in the text of the study reports and NDA Summary documents. In addition, the abbreviation for norelgestromin, NGMN, is used in the Physician's Insert included in this NDA.

During development of this product, RWJPRI planned to use the trademark, EVRA™. Upon further consideration, RWJPRI submitted the revised trademark, ORTHO EVRA™ to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for review. This submission, dated 18 April 2000, Serial No. 087 was reviewed by OPDRA and was given tentative approval on 02 October, 2000.

Ortho McNeil Pharmaceutical Drug Delivery Division

On 17 November 1999, Ortho-McNeil Pharmaceutical a company of Johnson & Johnson, acquired the drug delivery division of ——— .. including all the assets relating to the manufacturing of ORTHO EVRA. The name of the new Division is Ortho McNeil Pharmaceutical Drug Delivery Division (OMP DDD). (See Attachment 1)

FDA Agreements

The following major agreements were reached at the Pre-NDA Meetings held on 07 July 1999 and 27 July 1999 with members of the Division of Reproductive and Urologic Drug Products (DRUDP) and RWJPRI (Attachment 2):

- DRUDP agreed the preclinical program and oral NGMN/EE data is sufficient to support the NDA. No additional studies are required.
- DRUDP agreed the toxicology bridging data summarized in the background package was sufficient. Additional carcinogenicity studies would not need to be performed.
- PRI could cross-refer to oral contraceptive NDAs for Ortho-Cyclen (NDA 19-653) and Ortho Tri-Cyclen (NDA 19-697) for relevant human ADME reports. Additionally, PRI to provide clinical PK justification and quantitative information from the oral NGMN/EE clinical PK studies to demonstrate the comparability of norelgestromin from the oral contraceptives (containing norgestimate) to the contraceptive patch (containing norelgestromin).
- Efficacy results summarized in the background package are sufficient to support the NDA filing.
- Financial Disclosure information for only the pivotal studies: NRGEEP-CONT-002, 003 and 004 will be provided in this NDA.
- Pediatric Labeling Requirement for the NDA contains language previously provided for Ortho's marketed oral contraceptives. A request for waiver can be found in Item 20 of the NDA.

Electronic File Agreement

RWJPRI agreed to include the following items electronically on CD-ROM:

- Item 5 Nonclinical pharmacology/toxicology technical summary in Word
- Item 6 Human Pharmacokinetics and Bioavailability technical summary in Word; pharmacokinetic data in ASCII format.
- Item 8/10:
    - Clinical Study Report text for the Phase 3 studies: NRGEEP-CONT-002, NRGEEP-CONT-003 and NRGEEP-CONT-004 in Word
    - Clinical Pharmacology Summary
    - Background/Overview of Clinical Investigations
    - Integrated Summary of Efficacy

- Integrated Summary of Safety
- Integrated Summary of Risk/Benefit
- Case Report Forms in PDF format
- Data listings in ASCII format and datasets in SAS format

Additional Electronic Information

In addition to the above electronic agreements, the following items will also be provided:

- Item 2 Draft Labels/Labeling
- Item 3 Overall NDA Summary
- Item 4 Chemistry, Manufacturing and Controls information

For ease of review, the CD-ROM for each section is located in the first volume of the review copy of each Item. In addition to supplying Items 11 and 12 in the Clinical /Statistical Reviewer's Jacket, a CD-ROM is also located in the first volume of the Archival Copy of the NDA (NDA volume 1.001). Each CD is labeled with the NDA Item number(s) that it contains. An index of the contents of the CD-ROMs is included on each CD. All CD-ROMs have been scanned and deemed virus-free using McAfee Vshield program version 4.0.3, scan engine version 4.0.70, virus definition 4.0.4109.

Demonstration of Safety and Efficacy

Pursuant to 505(b)(1) of the Food, Drug and Cosmetic Act, the safety and efficacy data for ORTHO EVRA™ was established in clinical studies conducted by RWJPRI.

The principal source of safety data related to the use ORTHO EVRA™ in women was provided by three completed Phase 3 contraceptive efficacy and safety studies (Studies CONT-002, CONT-003, and CONT-004). Safety information was obtained from sexually-active women at risk of pregnancy, who were allocated to receive 6 to 13 cycles of treatment. A total of 3,330 subjects evaluable for safety received treatment for a total of 22,176 cycles in these three studies.

The principal source of effectiveness data was provided by six clinical studies. These included three Phase 2 studies (supportive data) and three Phase 3 studies. The three Phase 3 studies (Studies CONT-002, CONT-003, and CONT-004) were used to evaluate the contraceptive efficacy of ORTHO EVRA™. A total of 3,319 women from these three pivotal studies provided 22,160 cycles for evaluation of contraceptive efficacy, with 643 subjects completing 13 cycles of ORTHO EVRA™ use.

Physician's Package Insert/Patient Instructions

Item 2 Labeling contains the Physician's Insert (USPI) and Detailed Patient Information. Upon completion of labeling negotiations, the brief summary information will be drafted from the final detailed patient labeling. As per a 02 May 2000 telephone discussion with J. Mercier, FDA and V. Donnelly, RWJPRI, this was deemed acceptable.

Child-Resistant Closure

RWJPRI contacted the Consumer Product Safety Commission on 18 November 1999 to discuss packaging regulations for a transdermal contraceptive system. Per this conversation with Ms. Barone, it is our understanding that transdermal delivery systems are not subject to the requirements of the Poison Prevention Packaging Act (PPPA) provided in 16 CFR 1700. A copy of this Record of Contact is enclosed as Attachment 3.

Reviewer's Guides

An explanation of the content and organization of the NDA is located in the Overall NDA Reviewers' Guide contained in this volume. Each individual NDA Item (except Items 3 and 12) contains a separate NDA Item-specific Reviewers' Guide which provides more detail regarding that NDA Item's content and organization. We recommend that these Reviewers' Guides be consulted prior to review of this application to assist in understanding each technical sections' content and organization and to facilitate locating documents contained therein.

21 CRF 314.50(e)(2), Items to be Submitted in the Archival Copy

In accordance with 21 CFR 314.50(e)(2), RWJPRI has appended to the Archival Copy of the NDA the following Items:

- 3 copies of the Methods Validation (NDA Item 4c)
- 4 copies of the Draft Labels and Labeling (NDA Item 2)
- CD-ROM of the Case Report Tabulations:
    - ASCII Files for the Phase 2 and 3 studies (NRGEEP-CONT-001, 002, 003, 004, 005, 006, 007, 008)
    - SAS Datasets (in addition to the ASCII Files) for the Phase 3 studies (NRGEEP-CONT-002, 003, 004).
- CD-ROM in PDF format for the Case Report Forms for patients who died, discontinued due to an adverse event or became pregnant.

User Fee

The required User Fee of $285,740, payable to US FDA, was submitted under separate cover to Mellon Bank, Pittsburgh, PA on 07 December 2000 (User Fee No. 3894). A copy of this submission is provided in Item 18. The required User Fee Cover Sheet (Form FDA 3397) is signed and included in this application.

If you have questions regarding this submission prior to that time, please contact me at (908)704-4812, Valerie Donnelly at (908)704-5891 or call our telephone line dedicated for FDA use at (908)704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Cc: Ms. Jennifer Mercier, CSO

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: November 19, 2001 **Time:** 12:15 – 12:45 PM **Location:** Parklawn; 17B-43

NDA 21-180 **Drug:** ORTHO-EVRA (norelgestromin/ethinyl estradiol transdermal system)

Sponsor: R.W. Johnson Pharmaceutical Research Institute

Indication: Contraception

Type Of Meeting: Labeling

Meeting Chair: Dena Hixon, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Dena Hixon, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Davis, M.D. – Medical Officer, DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Dr. Gary Shangold - Regulatory Head of Drug Development , R.W. Johnson Pharmaceutical Research Institute
Dr. Ramon Polo - Director, Regulatory Affairs , R.W. Johnson Pharmaceutical Research Institute
Valerie Donnelly - Manager, Regulatory Affairs, R.W. Johnson Pharmaceutical Research Institute
Dr. George Creasy - Medical Monitor, Women's Health, R.W. Johnson Pharmaceutical Research Institute
Dr. Alan Fisher - Global Statistical Leader, R.W. Johnson Pharmaceutical Research Institute
Minnie Baylor Henry - Senior Director, Regulatory Affairs, R.W. Johnson Pharmaceutical Research Institute
Dr. James Oldham – Toxicologist, R.W. Johnson Pharmaceutical Research Institute
Dr. Larry Abrams - Global Clinical Pharmacokinetics Leader, R.W. Johnson Pharmaceutical Research Institute

Background:
NDA 21-180 was submitted on December 21, 2000. ORTHO EVRA consists of a progestin norelgestromin and, the estrogen ethinyl estradiol. ORTHO EVRA is a

combination transdermal patch that is applied once a week for three consecutive weeks followed by one patch-free week.

Purpose of the Meeting:
To discuss the proposed labeling for the Physician Insert and the Patient Package Insert.

Decisions Made:
- See attached label

Action Items:
- Fax meeting minutes to the sponsor within 30 days.

Minutes Preparer

Minutes Concurrence

Number of Pages Redacted 56

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Draft Labeling
(not releasable

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

/s/

Jennifer L. Mercier
11/20/01 12:10:39 PM
CSO

Daniel A. Shames
11/20/01 12:21:13 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: November 15, 2001 **Time:** 2:45 – 3:45 PM **Location:** Parklawn; 17B-43

NDA 21-180 **Drug:** ORTHO-EVRA (norelgestromin/ethinyl estradiol transdermal system)

Sponsor: R.W. Johnson Pharmaceutical Research Institute

Indication: Contraception

Type Of Meeting: CMC/Biopharmaceutics Meeting

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Amit Mitra, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. – Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Larry Abrams – Human Pharmacokinetics, R.W. Johnson
Valerie Donnelly – Regulatory Affairs, R.W. Johnson
Karen Futterknecht – Regulatory Affairs, R.W. Johnson
Eleanor Jeans – CMC Technical Writer, R.W. Johnson
Deepak Mehta – CMC, R.W. Johnson
Ramon Polo – Regulatory Affairs, R.W. Johnson
Asha Ramdas – Product Development, OMP-DDD, R.W. Johnson
Yinka Williams – CMC Leader, R.W. Johnson

Background:
NDA 21-180 was submitted on December 21, 2000. ORTHO EVRA consists of a progestin norelgestromin and, the estrogen ethinyl estradiol. ORTHO EVRA is a combination transdermal patch that is applied once a week for three consecutive weeks followed by one patch-free week.

Purpose of the Meeting:
To discuss the dissolution specifications and the data provided in the NDA required to support approval of this drug product.

Decisions Made:

- The Division is proposing the following dissolution specification for ORTHO EVRA™ after evaluating all the data presented in the NDA:

Ranges for % FS Dissolved

17 d-NGM				EE			
0.5 hr	*2.0 hr*	*8.0 hr*	*24 hr*	*0.5 hr*	*2.0 hr*	*8.0 hr*	*24 hr*

- The Division evaluated the individual data for the dissolution acceptance criteria.
- The reviewer evaluated the data and determined the acceptance criteria based on the mean ± 10%.
- This evaluation was based on individual data from the Phase 3 clinical batches, because these were the to-be-marketed formulations at production scale.
- All stability data were taken into consideration when evaluating the data and setting the acceptance criteria.
- If a specific lot does not meet the acceptance criteria at L1 stage, it still has a chance to meet the L2 requirement.
- The sponsor can use these acceptance criteria as an interim specification and revisit those acceptance criteria during the first year post-approval, if there is serious difficulty in meeting them.
- The Division has to work with the data that is presented in the NDA and cannot rely upon any models for assessment and review of this drug product. Unlike HRT transdermal patches, this drug product is a novel transdermal delivery system with a narrow therapeutic window and, therefore, the Division takes a more conservative approach in order to ensure continued efficacy of the product.

Action Items:

- Fax meeting minutes to the sponsor within 30 days.
- The sponsor will submit their response to the Division's proposal for the interim dissolution acceptance criteria by November 16, 2001.

Minutes Preparer

Minutes Concurrence

Post Meeting Note:

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Drafted: November 15, 2001
Initialed: Rumble11.16.01/Rhee11.16.01/Chatterjee11.16.01/Mitra11.19.01
Final: November 19, 2001

APPEARS THIS WAY
ON ORIGINAL

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/s/

Jennifer L. Mercier
11/19/01 02:22:04 PM
CSO

David T. Lin
11/19/01 02:57:12 PM
CHEMIST
I concur for MJRhee.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: November 9, 2001 **Time:** 2:35 – 3:00 PM **Location:** Parklawn; 17B-43

NDA 21-180 **Drug:** ORTHO-EVRA (norelgestromin/ethinyl estradiol transdermal system)

Indication: Contraception

Type Of Meeting: CMC/Biopharmaceutics Meeting

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Amit Mitra, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. – Clinical Pharmacology and Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Larry Abrams – Human Pharmacokinetics, R.W. Johnson
Valerie Donnelly – Regulatory Affairs, R.W. Johnson
Karen Futterknecht – Regulatory Affairs, R.W. Johnson
Eleanor Jeans – CMC Technical Writer, R.W. Johnson
Deepak Mehta – CMC, R.W. Johnson
Ramon Polo – Regulatory Affairs, R.W. Johnson
Asha Ramdas – Product Development, OMP-DDD, R.W. Johnson
Yinka Williams – CMC Leader, R.W. Johnson

Background:
NDA 21-180 was submitted on December 21, 2000. ORTHO EVRA consists of norelgestromin as the progestin and ethinyl estradiol as the estrogen. ORTHO EVRA is a combination transdermal patch that is applied once a week for three consecutive weeks followed by one patch-free week.

Purpose of the Meeting:
To discuss additional information needed to determine the dissolution specifications for this drug product.

Decisions Made:

- The Division is requesting the sponsor to send the data in item 4 of the NDA in an Excel spreadsheet in order to determine the dissolution specification for this drug product, mainly from lots 01107, 01517, and 01607.
- The Division has concerns regarding the proposed acceptance criteria for 8-hour time point.
- The sponsor needs to provide the history of the development of the media used for establishing the acceptance criteria of the *in vitro* release rates.

Action Items:

- Fax meeting minutes to the sponsor within 30 days.
- The sponsor will provide the data in item 4 of the NDA in an Excel spreadsheet format by Tuesday, November 13, 2001.
- The sponsor will provide the history and rationale for the choice of media for establishing the acceptance criteria for the *in vitro* release rates.

Minutes Preparer

Minutes Concurrence

Drafted: November 13, 2001
Initialed: Rumble11.13.01/Rhee11.15.01/Chatterjee11.15.01/Mitra11.15.01
Final: November 15, 2001

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

/s/

Jennifer L. Mercier
11/15/01 04:23:35 PM
CSO

Moo-Jhong Rhee
11/16/01 03:25:06 PM
CHEMIST
I concur

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

9 PAGES

(INTRA-AGENCY COMMUNICATIONS)