CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21040

CORRESPONDENCE

NDA 21-040

DEC 30 1998

R.W. Johnson Pharmaceutical Research Institute
Attention: David Goldberger, R.PH., M.S.
Assistant Director, Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Goldberger:

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

Name of Drug Products:	ORTHO-PREFEST (17 β-estradiol and norgestimate) 1 mg estradiol tablet and 1 mg estradiol/0.90 mg norgestimate tablet
Therapeutic Classification:	Standard (S)
Date of Application:	December 23, 1998
Date of Receipt:	December 24, 1998
Our Reference Number:	21-040

Unless we notify you within 60 days of our 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 February 22, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary User Fee goal date will be October 24, 1999, and the secondary User Fee goal date will be December 24, 1999.

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/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely,

/S/

12/30/98

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-040
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DLin
HFD-580/AJordan/KRaheja/LKammerman/AParekh
DISTRICT OFFICE

Drafted by: dm/December 30, 1998

filename: N21040AK.DOC

Concurrence:
LPauls 12.30.98

ACKNOWLEDGEMENT (AC)

NDA 21-040

SEP 22 1999

R.W. Johnson
Pharmaceutical Research Institute
Attention: Ramon Polo, Ph.D.
Associate Director, Regulatory Affairs
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Polo:

Please refer to your December 23, 1998, new drug application for ORTHO-Prefest (17 β-estradiol and norgestimate) Tablets, USP

We also refer to your submissions dated January 20, February 11, April 5, June 9 and June 24; 1999.

Our review of the Chemistry, Manufacturing and Quality Control section of your submissions is complete, and we have identified the following deficiencies:

1. Regarding the overage of estradiol, instead of using fixed overage %), the overage should be determined for each production batch based on the actual water content analysis data obtained from the batch of estradiol to be used.

2. Please provide the acceptance testing performed on the incoming batches of the drug substances (estradiol and norgestimate).

3. Please provide information on the holding time and storage conditions for the drug substance before being used in the manufacturing of the drug product.

4. Please provide the details of the sampling plan/procedure used for analytical testing of each drug product.

5. Please provide information on the holding time and storage conditions for the bulk drug product before blister packaging.

6. Please provide a sampling plan procedure for the container/closure system for the quality control analysis.

7. Regarding the drug product, the proposed specification of % for the norgestimate degradation products is not acceptable based on the available stability data. Please tighten the specification to %.

8. Please revise the stability commitment such that extension of expiry date is based on real-time data generated from the first three production batches after approval.

9. Please revise the storage statement in the package insert and immediate container and carton labels; it should read: Store at 25°C (77°F) excursion permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

10. Based on the available stability data, the tentative expiration date will be 18 months.

11. Please verify whether the following site is still involved in the finished product testing:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

/S/ 9/22/99

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for
Division of Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-040
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/MRhee/AAlHakim/TRumble
HFD-820/DNDC Division Director/JGibbs
DISTRICT OFFICE
Drafted by: dm/September 16, 1999
Initialed by: TRumble 09.20.99/AAlHakim, MRhee, MMann, LRarick 09.21.99
final: 9/22/99 MR
filename: N21040DR.DOC
DISCIPLINE REVIEW LETTER (DR)

/S/ 9/22/99

BY FACSIMILE TRANSMISSION
(Faxed on October 22, 1999)

Lisa Rarick, M.D., 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 21-040
ORTHO-PREFEST™
(17β-estradiol and norgestimate tablets)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the draft labeling information submitted with the original application on December 23, 1998, As a result of the comments that we have received from the Division today, we have revised the text of the Physician's Package Insert to incorporate the comments. The revised drafts (clean copy and strike-out/underline copy) are enclosed.

Also enclosed, but not revised, are the Patient Instructions (clean copy only). As a Phase 4 commitment, RWJPRI agreed today that the Patient Instructions will be revised in accordance with the plain English language document.

If you have questions regarding this information please contact me (908) 704-4812 or Valerie Donnelly at (908) 704-5891.

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

Enclosure: One Diskette containing Physician's Package Insert and Patient Instructions (strike-out/underline and clean copy versions to be stored in blue archival copy)

Desk Copy: Ms. Diane Moore, CSO, HFD-580

n:\e2ngm\ltr\final label 102299.doc/1

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

Sept 2, 1999
hand

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

FDA REQUEST FOR INFORMATION

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and recent requests (July 15, August 6, 14, and 16, 1999) from the Division for additional information concerning the review of the pending application. As a result, RWJPRI is providing this submission which contains the following items:

I. Request for Waiver: Pediatric Use Information (21 CFR 314.55)

A request for a full waiver of the requirement to provide Pediatric Use Information in the labeling for ORTHO-PREFEST is requested. To support this request, RWJPRI certifies that ORTHO-PREFEST does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. ORTHO-PREFEST is intended for use in the treatment of symptoms associated with the menopause. The drug product is not intended for use in humans below the age of 16 years (pediatrics), therefore, no clinical studies were conducted in this specific population.

II. ESTNRG-CHRT-102/103 Biopsy Readings

RWJPRI was asked if the 77 biopsies, identified in the study report for the 102/103 studies, were read by in-house personnel. We wish to explain the statement found on NDA page "Item 8/Item Volume 32/Page 36" which reads:

> "The readings were then obtained, employing the services of in-house clinical research personnel not associated with the study who handled the slides and who, like the pathologists, were blinded as to subject treatment assignments."

RWJPRI personnel did not participate in any pathology readings of endometrial biopsy slides. Data collection of the additional 77 biopsy

readings was managed by an independent RWJPRI task force – this was the only involvement by RWJPRI.

The procedures followed for obtaining efficacy readings for the 77 slides were identical to the procedures used originally as described in section 3.8.2.1. of the study report. The 77 slides were read by the same pathologists that participated in the original efficacy readings. The three pathologists who read the endometrial biopsy slides were

The 77 slides were read by
there was a discordance between the PA-1 diagnoses and the PA-2 diagnoses with respect to hyperplasia vs. non-hyperplasia, the slide was read by (PA-3) for arbitration. If

III. Revised Labeling: Physician's Insert

Prior to receipt of the Division's recommended changes to the Physician's Insert (received by fax on August 14, 1999), RWJPRI had intended to provide the Division with a revised draft insert to address editorial changes and specifically, to remove the Black Box from the insert. Upon the advice of Ms. Moore, RWJPRI deferred submission of the revisions until after receipt of the Division's recommended changes – these were subsequently received on August 14, 1999 by facsimile transmission. A brief teleconference was held at the Division's request on August 16, 1999. Additional insert changes were conveyed at the teleconference. We have reviewed and discussed the Division's recommended changes and are submitting the revised Physician's insert at this time; this includes RWJPRI's planned changes. There are some instances in which RWJPRI did not incorporate the Division's recommended changes – in those instances we have provided a brief explanation for our decision. To aid in the review of the revisions we are providing the following items behind the tab: "II. Revised Draft Labeling":

1. Draft Revised Physician's Package Insert (dated August 26, 1999): This copy is marked with Microsoft Word 7.0 "strikeout" and "underlined" text to indicate text which has been deleted (strikeout") and new text (underline), since the unannotated text was submitted in the original NDA on December 23, 1998. It may also be noted that the text has been numbered (1-29) to indicate for ease of reference, sections for which the Division had suggested changes or comments.
2. RWJPRI's numbered responses (1-29) which correlate to the numbered sequence on the Draft Revised Physician's Insert. We include responses to suggestions which were conveyed in the August 16 teleconference, but are not included in the August 14 fax.

3. A copy of the August 14, 1999 fax from the Division - this fax has subsequently been numbered to correlate with the responses from RWJPRI and the Draft Revised Physician's Insert.
4. Draft Revised Physician Insert on IBM 3 ½ inch diskette in WORD 7.0.

IV. Labeling: Label Components

We are providing color "mock-ups" of the following label components which were previously submitted in the original NDA, but as text only:

- Blister Card (front and back)
- Carton (Trade)
- Carton (Sample)
- Packer Tray
- Weekday Sticker and Weekday Sticker Instructions

If you have questions regarding this information please call me at (908) 704-4469, or Ramon Polo at (908) 704-4812.

Sincerely,
The R.W. Johnson
Pharmaceutical Research Institute

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

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

BY FACSIMILE TRANSMISSION
(faxed on October 20, 1999)

OCT 20 1999

Lisa Rarick, M.D., 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 21-040
ORTHO-PREFEST™
(17β-estradiol and norgestimate tablets)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the draft labeling information submitted with the original application on December 23, 1998, As a result of the comments that we have received from the Division on October 19, 1999, we have revised the text of the Physician's Package Insert as well as the Patient Instructions to incorporate the comments. The revised drafts are enclosed. We would like the Division to consider the following suggested changes:

1. **Description**. FDA requested at the October 6th , 1999 teleconference that we reconsider use of the word 'pulsed' in the description section of our Physician's Package Insert. In our written response of October 14th, RWJPRI expressed our desire to maintain the term 'pulsed', based upon previous consultations with physicians in the field. During the subsequent October 19th, 1999 teleconference, FDA proposed a different construction of this paragraph, incorporating the use of either 'cyclophasic' or 'cyclical' as the descriptors for the regimen. However, our same earlier research with physicians also tested the utility of these two terms in communicating the nature of the regimen. It was clear that the word 'cyclophasic' had no meaning to clinicians, and was confused with descriptors of multiphasic oral contraceptive regimens. Similarly, the term 'cyclical' was confused with sequential HRT therapies. Thus, while it was not our original preference, we would now prefer to return to the Division's earlier proposal, using the term 'intermittent', which was found to be the second most effective descriptor (after 'pulsed') in accurately communicating the nature of the ORTHO-PREFEST regimen to clinicians. We therefore suggest the following paragraph, which incorporates the Division's most recent reconstruction of the paragraph, in the Description section of the Physician's Package Insert.

> "The ORTHO-PREFEST regimen provides for a single oral tablet to be taken once daily. The pink tablet containing 1.0 mg estradiol is taken on days one through three of therapy; the white tablet containing

1.0 mg estradiol and 0.09 mg norgestimate is taken on days four through six of therapy. This pattern is then repeated continuously to produce the constant estrogen/intermittent progestogen regimen of ORTHO-PREFEST."

2. **Pharmacokinetics, Absorption**. FDA requested the inclusion of the sentence "Upon co-administration of ORTHO-PREFEST™ with a high fat meal, C_{max} for estrone and estrone sulfate were increased by 14% and 24% respectively and C_{max} for 17-deacetylnorgestimate was decreased by 16%". We propose the addition of "**The AUC values for these analytes were not significantly effected by food.**" at the end of your proposed sentence. Rationale, the indicated changes in C_{max} for analytes without information on AUC can be misleading since: (1) without explicit information, the effect on AUC is not clear, and (2) for HRT drugs administered chronically, AUC which is an estimate of the systemic exposure may be more meaningful than C_{max}.

3. **Pharmacokinetics, Drug-Drug Interactions**. FDA requested the inclusion of the sentences "A clinical study conducted in 36 healthy postmenopausal women indicated that the steady state serum estradiol levels during the estradiol plus norgestimate phase of the regimen may be lowered by 12-18%, as compared with the estradiol administered alone. The clinical relevance of these observations is unknown." RWJ PRI propose the addition of: "**The serum estrone and estrone sulfate levels during the estradiol plus norgestimate phase did not appear to decrease as compared with estradiol administered alone.**" Rationale: it may be misleading to indicate only partial results. It is impossible to know if lack of relevant information in the label could be interpreted to mean either no data or results that are unclear.

4. **Clinical Studies, Efficacy on Postmenopausal Symptoms.** The repetition of the sentences

"A clinical study conducted in 36 healthy postmenopausal women indicated that the steady state serum estradiol levels during the estradiol plus norgestimate phase of the regimen may be lowered by 12-18%, as compared with the estradiol administered alone. The serum estrone and estrone sulfate levels during the estradiol plus norgestimate phase did not appear to decrease as compared with estradiol administered alone. The clinical relevance of these observations is unknown."

in the 'clinical studies' section under table 2 is unnecessarily redundant, in particular because this section follows immediately after the 'drug-drug interactions' paragraph. RWJPRI plead for removal of the requested paragraph from the 'clinical studies' section.

5. **Clinical Studies, Efficacy on Vulvovaginal Atrophy**. Following FDA's suggestion, RWJPRI have included table 3. "Shifts in Maturation Index Following 7 Months Treatment with ORTHO-PREFEST or Estradiol.

Table 3: Shifts in Maturation Index[1] Following 7 Months Treatment with ORTHO-PREFEST™ or Estradiol

Treatment Group	N	Mean Shift (%)	Median Shift (%)
1 mg Estradiol	37	37.7	30
1 mg ORTHO-PREFEST™	32	47.0	45

1. Shift in Maturation Index is defined as percentage of vaginal mucosa cells maturing from parabasal to superficial.

Immediately preceding table 3. RWJPRI propose an introductory paragraph reading: "The effect of the estrogen component of ORTHO-PREFEST on vulvovaginal atrophy was confirmed in a 12-week placebo-controlled trial of healthy postmenopausal women with moderate to severe vasomotor symptoms (MSVS). The addition of norgestimate to estrogen (i.e., the ORTHO-PREFEST regimen) was studied in a 12-month trial in healthy postmenopausal women for endometrial protection. Results from a subset population (n=69) with paired tests for maturation index of the vaginal mucosa are shown in table 3."

6. **Clinical Studies, Effects on the Endometrium.**
Following FDA's suggestion, RWJPRI have included immediately under table 4."In another 12-month controlled clinical trial for endometrial protection an additional 190 postmenopausal women were treated with ORTHO-PREFEST. No subject had a diagnosis of endometrial hyperplasia after treatment."

7. **How Supplied.**
Largely following FDA's suggestion, but with some modification, RWJPRI have reworked the opening of this paragraph and propose it to read: **"ORTHO-PREFEST is available as two separate round-shaped tablets for oral administration, supplied in a blister card with the following configuration: 3 pink tablets, followed by 3 white tablets for a total of 30 tablets per blister card."**

8. **Pharmacokinetics, Excretion.** FDA asked us to indicate the study that support the 37 hour half-life for 17-deacetylnorgestimate in the 'Pharmacokinetics, Excretion' section. The answer is: study ESTNRG-PHI-008.

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

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ FAX ☐ MEMO

CSO INITIALS DATE

Desk Copies: Ms. Diane Moore, CSO, HFD-580 and Dr. Moo Jhong Rhee, chemistry reviewer, HFD-580

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

BY FACSIMILE TRANSMISSION
(Faxed on October 14, 1999)

OCT 15 1999

Lisa Rarick, M.D., 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, MD 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION/AMEND-AMENDMENT TO A PENDING APPLICATION
Biopharmaceutical, CM&C and Clinical

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and recent requests (September 30th and October 6th, 1999) for additional information concerning the review of the pending application. This submission contains our responses to FDA's requests as well as amendments to the NDA. The FDA requests are in bold text, followed by RWJPRI's responses.

September 30th Biopharm requests:

1. Please provide plots of invitro dissolution data for the clinically tested 0.5 mg & 2 mg estradiol RWJ tablets to the to-be-marketed 1 mg estradiol ORTHO-PREFEST tablets.
This information is provided behind the tab titled Attachment 1.

2. Please provide f_2 dissolution similarity factor values for the to-be marketed 1 mg estradiol ORTHO-PREFEST tablets to the clinically tested 0.5 mg & 2 mg RWJ estradiol tablets.
This information is provided behind the tab titled, Attachment 2.

3. Please provide plots of invitro dissolution data for the clinically tested (safety and efficacy) 1 mg estradiol + 90 mcg norgestimate ORTHO-PREFEST tablets to the to-be-marketed 1 mg estradiol + 90 mcg norgestimate ORTHO-PREFEST tablets.
This information is provided behind the tab titled, Attachment 3.

4. Please provide f_2 dissolution similarity factor values for the to-be-marketed 1 mg estradiol + 90 mcg norgestimate ORTHO-PREFEST tablets to the clinically tested 1 mg estradiol + 90 mcg norgestimate ORTHO-PREFEST tablets.
This information is provided behind the tab titled Attachment 4.

October 6th CM&C Requests:

1. (Overage of Estradiol, USP in ORTHO-PREFEST Tablets)
At our teleconference with the Division on October 6, 1999, Dr. Rhee stated that he was not comfortable with our choice of % standard water adjustment. He asked if we could use an interim approach of adjusting water based on the actual assay results for the first 10-20 batches of drug substance and then when we had developed a database we could go with a standard adjustment.
Dr. Falzone replied that subsequent to our response to the item we had obtained water data on more than forty lots of material from and could use that information as a database for the water adjustment.
Dr. Rhee requested that we provide him with the information, which should include both the water assay results and the date of manufacture of the batches.
Response

At this time we would like to **amend the NDA** to include Table 1 (Attachment 5). This table lists the water content data for 38 lots of Estradiol, USP produced by over the past eighteen months. The average water content of the data is %. Data generated on the estradiol lots used in Ortho's PREFEST development program also show an average water content of % (Table 2 [Attachment 6]). This data support the average water adjustment of %, as a way to maintain a standard production operation while insuring that the patient receives the intended therapeutic dose of Estradiol, USP.

2. Dr. Rhee asked if the expiration dating of the drug product would include the six months of storage that we had proposed for the bulk tablets.
The bulk tablet expiration dates are determined from the date of manufacture. The finished drug product, which contains two tablet lots in the PVC blister, will have the shorter expiration dating of these two tablet lots. At this time we would like to **amend** the NDA Specification/Analytical Methods sections 2.6.1.1 and 2.6.2.1, for both 17β-Estradiol, USP and Norgestimate, to include the following statement:

> "Each batch of drug substance is annually reassayed through the expiration dating period of three years".

3. Dr. Rhee stated that he had not been able to get any response to his inquiries on the Norgestimate Drug Master File No.
On October 8th, 1999 RWJPRI provided Ms. Diane Moore with the following scientific contact:

It is RWJPRI's understanding that is addressing all items identified by the FDA directly with them.

October 6th Clinical Request:

At our teleconference with the Division on October 6, 1999, Dr. van der Vlugt asked if the endometrial biopsy safety readings in Study 102/013 were all performed in the same laboratory. RWJPRI responded that they were. Dr. van der Vlugt then asked whether in that case, the biopsies were all read by the same pathologist and whether this was one of the pathologists who read the efficacy readings as well or a separate pathologist. RWJPRI responded that the safety readings were done by a number of pathologists, but all in the same laboratory, asked RWJPRI to provide verification of this.

Verification of the above information is provided as follows: was the central pathology laboratory used for baseline and on-treatment specimens for Study 102/103. Each safety reading was performed in a blinded manner by one of the five pathologists employed at this laboratory

These safety readings were performed immediately by a single pathologist to establish the presence or absence of hyperplasia. The safety readings were performed on an ongoing basis, beginning with fourth quarter 1995 recruitment and enrollment activities.

The efficacy readings began in the fourth quarter 1997. All slides were read in a blinded manner for efficacy by three pathologists with a recognized expertise in endometrial histology

evaluated all of the slides for efficacy. Whenever the evaluation of the two readers was not identical with respect to the presence or absence of hyperplasia, an arbitrator also reviewed the slides. The pathologists could not identify subject numbers or treatment assignments, and did not know the results of other pathologists' readings. Also, the efficacy and safety readings were clearly separated in time.

Please contact me at (908) 704-4812 or contact Valerie Donnelly at (908) 704-5891 if you have questions regarding this information.

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

REVIEWS COMPLETED

CSO INITIALS DATE

Desk Copy: Ms. Diane Moore, CSO, HFD-580

ORIGINAL
ORIG AMENDMENT
BC

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

BY FACSIMILE TRANSMISSION
(Faxed on October 5, 1999)

OCT 15 1999

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION
Chemistry, Manufacturing
and Controls

Dear Dr. Rarick:

Reference is made to FDA's correspondence dated September 22nd, 1999, which contained the comments of the Chemistry Team Leader, Dr. Moo-Jhong Rhee. This submission contains our responses to FDA's comments, in the order in which they were presented. The FDA comments are in bold text, followed by our responses.

1. Regarding the overage of estradiol, instead of using fixed overage %), the overage should be determined for each production batch based on the actual water content analysis data obtained from the batch of estradiol to be used.

Using an average adjustment for water content based on the theoretical amount of water in an active component allows for consistency in operation standards while providing the intended dose of active component to the patient. In the case of estradiol the theoretical water content of the compound is .% as reflected in the USP water specification. Monitoring of the actual water content using the USP specified Karl Fischer test method in the batches received during development illustrated that the % theoretical adjustment would result in an adjustment higher than the average water content seen for the material. In an effort to deliver 100% of the active dose to the patient with the minimal adjustment for water content the adjustment of % was recommended.

After reviewing the history of similar adjustments in other products it was determined that the USP specification with an open lower range would not be adequate to provide control of the adjustment for water of hydration. An in house specification of

% moisture has been established for estradiol. This new specification controls the moisture level to within a % variation. Taking into consideration the variability of the water analysis test method and the variabilities associated with delivering an active component in a tablet dosage form, the % average adjustment provides a reasonable and standard means of adjusting for the water of hydration to deliver 100% of the active dose to the patient.

2. Please provide the acceptance testing performed on the incoming batches of the drug substances (estradiol and norgestimate).

17β-Estradiol, USP

purchases 17β-estradiol (E2) from and receives each lot of drug substance with a Certificate of Analysis (C of A), confirming compliance to the USP requirements. Upon receipt, conducts complete release testing of the drug substance according to the official release specifications and test methods for E2. These specifications and test methods are presented in Section 2.6 of the Chemistry, Manufacturing and Controls Section of the NDA.

Following appropriate validation, may choose to accept the 17β-estradiol drug substance upon a C of A with confirmation identity testing, according to the provisions of 21CFR211.84(d)(2), or may choose to conduct complete release testing.

Norgestimate

purchases norgestimate from and receives each lot of drug substance with a Certificate of Analysis. Upon receipt, conducts complete release testing of the drug substance according to the official release specifications and test methods for norgestimate. These specifications and test methods are presented in Section 2.6 of the Chemistry, Manufacturing and Controls Section of the NDA.

Currently, the specifications and test methods employed by for the release of norgestimate are those provided in their DMF is currently implementing the official norgestimate specifications and test methods presented in our NDA 21-040 (Section 2.6 of the Chemistry, Manufacturing and Controls Section).

Following complete implementation of the official regulatory drug substance specifications and test methods by the appropriate validation will be

conducted. may then choose to accept the norgestimate drug substance upon a C of A, with confirmation identity testing according to the provisions of 21CFR211.84(d)(2), or may choose to conduct complete release testing.

3. Please provide information on the holding time and storage conditions for the drug substance before being used in the manufacturing of the drug product.

The holding time for both 17β-estradiol and norgestimate is three years. The storage condition of both active ingredients is °F, with % relative humidity.

4. Please provide the details of the sampling plan/procedure used for analytical testing of each drug product.

The sampling plan used by the manufacturer of the 1.0 mg Estradiol Tablet, USP and the 1.0 mg Estradiol/90 µg Norgestimate Tablet,
, for analytical testing of each drug product batch follows.

Bulk Tablet Composite Sample

a. Not less than 50 tablets per drum will be taken. This number is based on 30 drums per batch. For batches or parts of batches with fewer than 30 drums, the tablets per drum number must be adjusted so that the total number of tablets sampled is at least 1500.

b. Samples will be taken from each drum after all Processing inspections have been completed.

c. The sample container will be marked with the dosage form, batch number, the drums represented in the sample, sampling date and sampler's initials.

All samples indicated above will be submitted to Quality Assurance for Analysis.

Individual Drum Samples

a. Not less than 30 tablets per drum will be taken.

b. Samples for testing (when using plastic drums): The samples for testing will be chosen from the total number of drums in the batch according to the sampling chart (Refer to **Attachment 1**). If a drum identified by the chart will not be included in the batch, sample from the next or previous drum in sequence. There must be no less than 10 different drum samples submitted for analytical testing.

c. Samples for testing (when using stainless steel drums): Thirty (30) tablets per drum should be taken from each stainless steel drum even if there are less than 10 different drums.

d. Each sample container will be marked with the dosage form, batch number, drum number, sampling date and sampler's initials.

All samples indicated above will be submitted to Quality Assurance for Analysis.

Microbiological Samples

Tablets submitted for microbiological testing will be collected into a sterile container, from the beginning, middle and end of the tabletting process to yield one composite sample of approximately 100 grams. Mark the sample container with product name, dosage form, batch number, date sampled, sampler's initials, and sample weight.

5. Please provide information on the holding time and storage conditions for the bulk drug product before blister packaging.

The holding time studies for granulation and tablets are currently being validated using an approved protocol. One batch of the 1.0 mg Estradiol Tablet, USP and one batch of the 1.0 mg Estradiol/90 µg Norgestimate Tablet will be used to complete this study. A report will be issued following completion of the study. Each granulation will be validated for storage in the hopper for a 30-day period. The tablets will be validated for storage in double polyethylene bags which are placed in [1]nitrogen purged, heat sealed aluminum bags in fiber drums for a 6 month period.

The storage conditions are as follows:

	Temperature	**Relative Humidity**
Granulation	Approximately 65° - 70°F (average) The storage area not to exceed 85°F	Approximately 30%, not exceeding 40%
Tablets	The average temperature condition for this area is approximately 70 to 75°F	Approximately 80%

6. Please provide a sampling plan procedure for the container/closure system for the quality control analysis.

The quality of foils and films is subject to the Acceptable Quality Levels for Military Standard Sampling Procedures for Inspection by The

[1] Nitrogen purge used only for the storing of E2/norgestimate tablets.

components are received, sampled, and inspected using approved specifications and standard operating procedures. The sampling selection used from each of these component shipments which consist of rolls is the square root plus one.

7. Regarding the drug product, the proposed specification of % for the norgestimate degradation products is not acceptable based on the available stability data. Please tighten the specification to %.

The major degradation product detected in the drug product is norgestrel acetate. A maximum value of % (Lot D-98-0072-A) was observed at 3-months at 100 foot candles, % RH, and % (Lot D-98-0072-A) at 12 months for storage at % RH. The R.W.J. Pharmaceutical Research Institute is amending the finished drug product specifications to include the tightening of the norgestrel acetate specification and the total impurities specification from %.

8. Please revise the stability commitment such that extension of expiry date is based on real-time data generated from the first three production batches after approval.

The stability commitment has been updated to include the extension of the expiration-dating period based on data generated at % RH from the first three-marketed product batches of 1.0 mg Estradiol Tablet, USP and 1.0 mg estradiol/90µg norgestimate tablet. The update to Section 3.8.4 of the Chemistry, Manufacturing and Controls Section of NDA 21-040 (Extension of the Expiration Dating Period) is presented below.

EXTENSION OF THE EXPIRATION DATING PERIOD

Extension of the expiration-dating period will be based on data generated at % RH from the first three-marketed product batches of 1.0 mg Estradiol Tablet, USP and 1.0 mg estradiol/90µg norgestimate tablets. All data must conform to the proposed finished drug product specification, as presented in Section 3.6.

9. Please revise the storage statement in the package insert and immediate container and carton labels; it should read: Store at 25°C (77°F) excursion permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

The storage statement in the package insert and carton labels will be revised as requested. Due to limited space and font size issues, and in an effort to keep the storage statement on the front of the immediate container, we would like to have "Store at 25°C (77°F) (see insert)" remain on the front of the immediate container.

10. Based on the available stability data, the tentative expiration date will be 18 months.

The tentative expiration date for this drug product has been accepted by The R. W. J. Pharmaceutical Research Institute to be 18 months when drug product is stored at 25°C (77°F) with excursions permitted to 15-30 °C (59-86 °F).

11. Please verify whether the following site is still involved in the finished product testing:

The above facility is involved in the initial warehousing and distribution of finished drug product. It is not involved in the finished product testing of 1.0 mg Estradiol Tablet, USP and 1.0 mg estradiol/90µg norgestimate tablet. Please refer to Section 3.4.2 of the Chemistry, Manufacturing and Controls Section of NDA 21-040 (Manufacturer, Other Facilities) for additional details.

Please contact me (908) 704-4812 or Valerie Donnelly at (908) 704-5891 if you have questions regarding this information.

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible]

CSO INITIALS DATE

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ORIGINAL

ORIG AMENDMENT

BL

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

BY FACSIMILE TRANSMISSION
(Faxed on October 14, 1999)

OCT 15 1999

Lisa Rarick, M.D., 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 21-040
ORTHO-PREFEST™
(17β-estradiol and norgestimate tablets)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the draft labeling information submitted with the original application on December 23, 1998, As a result of the comments that we have received from the Division over the past several weeks, we have revised the text of the Physician's Package Insert as well as the Patient Instructions to incorporate the comments. The revised drafts are enclosed. We would like the Division to reconsider the following suggested changes:

1. Table 3 in the Physician's Package Insert is titled, "Incidence of Endometrial Hyperplasia (ITT population) at End of Treatment in Two 12-Month Clinical Trials of ORTHO-PREFEST™. FDA requested that we add to the second row heading in Table 3, "Total No. Evaluable Biopsies **at month 12**". At this time we request that the heading remain as it reads, "Total No. Evaluable Biopsies", as this more accurately describes the population. The title of the table describes 'end of treatment' because the table reflects an intent-to-treat population. This population included the last biopsy for all subjects with on-treatment biopsies, whether or not the subjects completed 12 months of treatment.

2. FDA requested that we reconsider use of the word 'pulsed' in the description section of our Physician's Package Insert. RWJPRI would like to maintain the term 'pulsed'. Previous extensive consultations with physicians in the field, revealed that this term most accurately described the progestin dosing of our regimen. It was specifically conveyed that the descriptor 'intermittent' connoted randomness and irregularity. We suggest use of the following paragraph in the Description section of the Physician's Package Insert.

CENTER FOR DRUG EVAL. & RES.
OCT 18 1999

"This constant estrogen/pulsed progestogen regimen consists of a pattern of three days of estradiol-only followed by three days of estradiol plus norgestimate."

3. We distribute a large line of oral contraceptives which are labeled in a way that reflects class labeling on the issue of estrogen associated risks for thromboembolism. The existing class labeling for menopausal Hormone Replacement Products already addresses the increased risk for thrombosis in users who do not have identifiable risk factors. We thus feel that we would be ignoring the medical needs of ORTHO-PREFEST™ users who have a risk factor (i.e. elective surgery), by removing the following statement from the Physician's Package Insert.

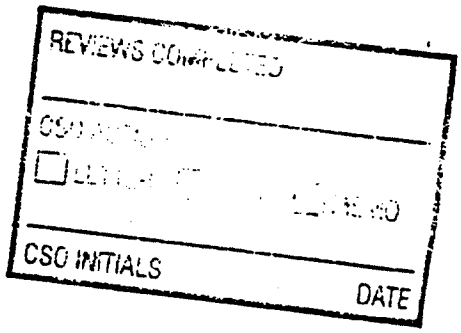
We have removed that statement from the ORTHO-PREFEST™ label, as you have directed us to do in the October 6th, 1999 teleconference. However, we would ask the Division once again to reconsider the inclusion of this statement in this final label.

If you have questions regarding this information please contact me (908) 704-4812 or Valerie Donnelly at (908) 704-5891.

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

Desk Copy: Ms. Diane Moore, CSO, HFD-580



ORIGINAL

ORIG AMENDMENT

BM

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

OCT 15 1999

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to FDA's verbal requests on September 24th for additional clinical information. The information below was faxed to Ms Diane Moore on October 6th, 1999. In a follow-up telephone conversation, we informed Ms. Moore that the subject number under Randomization 2, should be 58011, not 58001. As noted below with the highlight and strikeout feature, the subject number has been corrected. The original FDA requests are in bold text, followed by our responses.

In addition we are providing a revised version of the Weekday Sticker Instructions, behind the tab titled, Attachment 1. The original Weekday Sticker Instructions may be found on page 01 00091 of the submission dated September 2, 1999. A black and white copy is provided with this submission for ease of review (see Attachment 1a). Subsequent to the September 2nd submission, FDA requested that RWJPRI remove the word, 'HRT' from Number 1 and replace it with the product name, Ortho-Prefest™ (see color copy Attachment 1b).

SEPTEMBER 24TH REQUESTS:

1. STUDY 104:

Randomization 1/subjects who withdrew from the study -reason why

a. Identify the six subjects who withdrew due to 'adverse event' and identify the adverse events.

Subject Number	Adverse Event(s)
5005	Leg cramping
20004	"MVA" (motor vehicle accident)
2006	Mood Swings
	Fatigue
	Insomnia

Subject Number	Adverse Event(s) (continued)
13002	Crying Episodes
1006	Hives
	Increased heart rate
	Chest pressure
14001	Sinus Congestion
	Headaches

b. Identify the four subjects who withdrew due to 'subject choice' and identify what 'subject choice' meant for each subject.

Subject Number	Subject Choice comment (if any)
5002	no reason specified
13005	no reason specified
14005	no reason specified (subject had migraine headaches during study and migraine present in medical history)
19003	hot flashes

2. STUDY 104:

Randomization 2/subjects who withdrew from the study-reason why

a. **Identify the four subjects who withdrew due to 'adverse event' and identify the adverse events.**

Subject Number	Adverse Event
~~58001~~58011	Migraine
58007	Cancer of the Right Upper Lobe Cavity
64001	Gastrointestinal Upset
60006	Hair Loss

b. **Identify the seven subjects who withdrew due to 'subject choice' and identify what 'subject choice' meant for each subject".**

Subject Number	Subject Choice Comment (if any)
47007	no reason specified
48002	"went back on previous treatment - estrace"
48003	"wanted to discontinue due to treatment failure"
56012	no reason specified
56015	no reason specified
54006	"lack of efficacy"
60003	no reason specified

SEPTEMBER 30TH REQUEST:

Were the endometrial biopsy safety readings conducted by an on-site local pathologist? If not, who completed the safety readings?

Study ESTNRG-CHRT-102/103:

All biopsy specimens (baseline and on-treatment) were sent to a central laboratory for processing and for the initial safety reading.

(Previously submitted to NDA 21-040 on December 23, 1998, Item 8/Item Volume 32/Page 35)

Study N93-072:
All biopsy specimens were sent to the where they were processed. All biopsies underwent two assessments, one for safety and one (which involved multiple readings) for efficacy. The safety assessment was done on an ongoing basis at results were reported immediately to the investigators. Based on the safety reading, subjects with hyperplasia at pretreatment were not to be enrolled in the study; subjects with hyperplasia on treatment were to be discontinued from treatment.
(Previously submitted to NDA 21-040 on December 23, 1998, Item 8/Item Volume 120/Page 32)

Study CC-2636-C-101:
Preparations were to be categorized by 'Insufficient tissue', 'cancer', 'hyperplasia' (with subtypes simple, complex, with/without atypia') or 'normal'. The first reading was on an ongoing basis by one pathologist

Endometrial hyperplasia or cancer detected at baseline made the subject ineligible for study participation. Subjects with hyperplasia or cancer detected in on-treatment biopsies were to be immediately excluded from the study.
(Previously submitted to NDA 21-040 on December 23, 1998, Item 8/Item Volume 157/Page 19)

Study ESTNRG-CHRT-105:
Endometrial biopsies were prepared for histologic analysis on an ongoing basis and were evaluated by one pathologist who was blinded to treatment

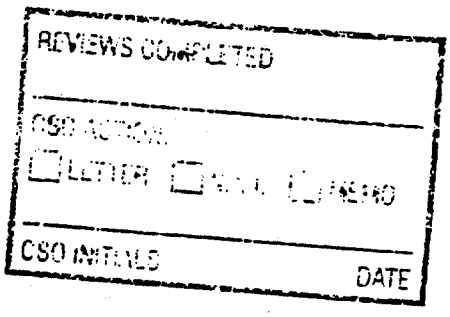
(Previously submitted to NDA 21-040 on December 23, 1998, Item 8/Item Volume 165/Page 16)

RWJPRI confirms that all safety endometrial biopsy readings for Studies C-101 and 105 were performed by

Please contact me at (908) 704-4812 or contact Valerie Donnelly at (908) 704-5891 if you have questions regarding this information.

Sincerely,

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs



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ORIGINAL

NEW CORRESP

NC

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

OCT 15 1999

Lisa Rarick, M.D., 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 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

OTHER:
General Correspondence

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the telephone conversations with FDA and RWJPRI on October 5th and October 6th, 1999. The purpose of the telephone conversations with the Division was to discuss an issue concerning findings in the Clinical Pharmacology section of the proposed draft of the USPI, under Population Pharmacokinetics, Special Populations, prior to our scheduled teleconference with the Division on October 6, 1999. Attached for your review is a copy of our Record of Contact No. 99-32. We have tried to be comprehensive in including all of the details of our three conversations with you on October 5th and 6th which we could recall, recognizing that you will likely wish to edit these appropriately in preparing an official Record of Contact from these notes.

Please contact me at (908) 704-5148 if you have questions regarding this information.

Sincerely,

Gary Shangold, M.D.
Vice President
Regulatory Franchise Leader

REVIEWS COMPLETED
ORIG ACTION
☐ APPR ☐ ☐ MEMO
OSE INITIALS DATE

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DUPLICATE
DRUG AMENDMENT

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

SEP 24 1999

Lisa Rarick, 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 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

Other: Final Safety Update

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ submitted on December 23, 1998, for hormone replacement therapy and prevention of osteoporosis. In accordance with 21 CFR 314.50(5)(d)(vi)(b) we are submitting the Final Safety Update for ORTHO-PREFEST. This submission, consisting of one volume, includes safety data available from the clinical data base for the time period February 19, 1999 to August 6, 1999. During this time period there were three ongoing studies with ORTHO-PREFEST:

. As requested, the Clinical and Statistical data were also faxed to Diane Moore at FDA on September 23, 1999; a copy of the fax confirmation form is also enclosed with this submission.

This submission contains the following information:

	Item Volume	Page Number
Index	1	
Clinical and Statistical Data	1	01 00001
Case Report Forms for Study ESTRNG-CHRT-106	1	01 00076

Please contact me at (908) 704-4812 or call our telephone line dedicated for FDA use at (908) 704-4600 if you have questions regarding this submission.

Sincerely,

Valerie A Connelly for/

Ramon Polo, Ph.D.
Associate Director
Regulatory Affairs

N:\E2NGM\LTR\99031PMJ.DOC\24 September, 1999\vd\1

ORIGINAL

ORIG AMENDMENT

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

BY FACSIMILE TRANSMISSION

August 9, 1999

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and
17β-estradiol/norgestimate tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION
Clinical
Human Pharmacokinetics

Dear Dr. Rarick:

Reference is made to the request of August 3, 1999 for additional information concerning the pending NDA for ORTHO-PREFEST™ (NDA 21-040). In a teleconference between representatives of the Division of Reproductive and Urologic Drug Products, FDA (Dr. Ameeta Parekh, Dr. Theresa van der Vlugt and Ms. Diane Moore) and The R.W. Johnson Pharmaceutical Research Institute (Dr. Ramon Polo and Ms. Valerie Donnelly), we were requested to provide additional information and analyses for the Clinical and Human Pharmacokinetics sections, respectively.

Clinical

Dr. van der Vlugt requested additional analyses of the data from the 104 and 102/103 studies for weeks 4, 8 and 12. This information was previously faxed to the Division on Friday, August 6, 1999. It is included with this submission for completeness

Human Pharmacokinetics

Dr. Parekh requested an additional analysis of the data from the pharmacokinetic study ESTNRG-PHI-001. Specifically, we were requested to provide 90% confidence intervals for log-transformed AUC and C_{max} (bioequivalence testing) for baseline corrected and uncorrected estradiol (E_2), estrone (E_1) and estrone sulfate (E_1S) as follows:

1:1/30	1:1/90
Day 87 vs. Day 90	
Day 87 vs. Day 87	
Day 90 vs. Day 90	

Human Pharmacokinetics (cont'd.)

Results of the analysis show that the two regimens are bioequivalent for all three comparisons (Day 87 vs. Day 90, Day 87 vs. Day 87, and Day 90 vs. Day 90) for E_2 and E_1, if intra-subject variability was used in the calculation (Table 1). The 90% confidence interval for E_1S slightly exceeded the 80-125% bioequivalence criteria limits (Table 1). Bioequivalence was demonstrated for both baseline-corrected and baseline uncorrected E_2 and E_1. Generally, a cross-over study design and intra-subject variability are used in bioequivalence testing.

ESTNRG-PHI-001 employed a parallel-group design as it was intended to provide multiple-dosing pharmacokinetic information hence, the ANOVA modeling of the data should utilize inter-subject variability in the calculation of 90% confidence interval (Table 2). Intra- and inter-subject variabilities of ESTNRG-PHI-001 are presented in Table 3.

Since it is intra-subject variability that should be used in the 90% confidence interval bioequivalence testing, we believe the analysis presented in Table 1 is more appropriate. This is to say that the two regimens, 1:1/30 and 1:1/90 are bioequivalent for E2 and E1.

Please contact me at (908) 704-4469 if you have questions regarding this information.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

LETTER PMA MEMO

CSO SIGNATURE DATE

ORIGINAL

NEW CORRESP
~~DRUG~~ AMENDMENT

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

JUN 24 1999

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and norgestimate tablets)

AMENDMENT TO A PENDING APPLICATION
Chemistry, Manufacturing and Controls Information

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to our Pre-NDA Meeting of March 31, 1998 under IND Chemistry, manufacturing and controls issues were discussed at the noted pre-NDA meeting; among the issues was our proposal to submit additional stability data for the drug substances and drug product. Drs. David Lin and Moo-Jhong Rhee, FDA, agreed that submission of additional stability data would not add more time to the review clock as long as the data was submitted within six months of the original NDA. The additional stability data for the drug substances estradiol and norgestimate, and the drug products estradiol tablets and estradiol/norgestimate tablets is provided with this submission.

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.

Please contact me at (908) 704-4469 if you have questions regarding this information.

Sincerely,

Please send this to Dr. Ali Al-Hakim at HFD-180.
7/9/99

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

NDA SUPP AMEND
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ORIGINAL

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

JUN - 9 1999

Diane Moore, CSO
Division of Reproductive and Urologic
Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™
(17β-estradiol and norgestimate tablets)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Ms. Moore:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the draft labels submitted with the original application on December 23, 1998, and subsequently revised and submitted on April 5, 1999. As a result of the preliminary comments we received from the Division on April 19, 1999 by teleconference, we have revised the draft blister card to accommodate the suggested revisions. The revised draft, color label of the proposed blister card for the finished drug product is enclosed. It is a 1:1 ratio text mock-up of the blister card label, both back and front. This draft label is being forwarded to you at this time to gain preliminary review of the revised formatting and text. We have incorporated the following suggested changes:

- Tablet strengths added to front of blister card: "1 mg estradiol and 1 mg/0.09 mg norgestimate"
- "Package not child-resistant" added to front of blister card

I will contact you in two weeks to obtain your comments. Four copies of the draft blister card label are attached. If you have questions regarding this information please contact me at (908) 704-4469.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

Enclosures (4)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL

ORIG AMENDMENT

PHARMACEUTICAL RESEARCH INSTITUTE

MAY 5 1999 HFD-580 DRUG EVALUATION AND RESEARCH

APR 30 1999

BY FACSIMILE TRANSMISSION

Lisa Rarick, 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

AMENDMENT TO A PENDING APPLICATION
Human Biopharmaceutics

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to a teleconference between representatives from The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and FDA on April 5, 1999. The discussion covered issues raised by Drs. Jarugula, Lau, and Parekh, Division of Biopharmaceutics, FDA, concerning data submitted to support our osteoporosis claim. As a result of the discussion, RWJPRI was asked to summarize information available from the literature and internal study reports concerning estrogen induction of SHBG and the potential influence of norgestimate.

We have completed the requested summary and are submitting the information along with references that were not previously submitted to the NDA. As discussed with Ms. Diane Moore, CSO, we are submitting this information as an amendment to the application, however, it is primarily a response to a FDA request for information, as noted.

If you have questions regarding this information please contact me at (908) 704-4469.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL

ORIG AMENDMENT

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

APR 23 1999

Lisa Rarick, 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

NDA ITEM 9:
Four Month Safety Update

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ submitted on December 23, 1998, for hormone replacement therapy and prevention of osteoporosis. In accordance with 21 CFR 314.50(5)(d)(vi)(b) we are submitting the Four Month Safety Update for ORTHO-PREFEST. This submission, consisting of 5 volumes, includes safety data available from the clinical data base for the time period June 30, 1998 to February 19, 1999. During this time period there were three ongoing studies with ORTHO-PREFEST:

This submission contains the following information:

	Item Volume	Overall volume
Index	1	1.001
Clinical and Statistical Data	1-2	1.001 - 1.002
Case Report Forms	1-3	1.003 - 1.005

Please contact me at (908) 704-4469 if you have questions regarding this submission.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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DUPLICATE
ORIG AMENDMENT
12

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

APR - 5 1999

Diane Moore, CSO
Division of Reproductive and Urologic
Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

AMENDMENT TO A PENDING APPLICATION
Labels/Labeling Information

Dear Ms. Moore:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to the draft labels submitted with the original application on December 23, 1998. We are amending NDA 21-040 with a draft, color label of the proposed blister card for the finished drug product. The draft label, enclosed, is a 1:1 ratio text mock-up of the blister card label, both back and front. The text is based upon the text submitted in NDA Item 2, Item volume 2, page 31. This draft label is being forwarded to you at this time to gain a preliminary review of the text and text-formatting planned. I will contact you in two weeks to obtain your comments. Four copies of the draft blister card label are attached.

If you have questions regarding this information please contact me at (908) 704-4469.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

Enclosures (4)

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ORIGINAL

NEW CORRESP

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

FEB 11 1999

Diane Moore, CSO
Division of Reproductive and Urologic
Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestim

AMENDMENT TO
PENDING APPLICATION
Trademark Information

Dear Ms. Moore:

With reference to your request of February 8, 1999 regarding NDA 21-040, we are amending this pending application with trademark information. The original application, submitted December 23, 1998, provided for the trademark "ORTHO-PREFEST"; it was noted, however, that "PREFEST" was the trademark submitted to the Division on May 18, 1998 (serial no. 072) under IND for consideration by the Labeling and Nomenclature Committee (LNC). The LNC subsequently deemed the chosen trademark "PREFEST" acceptable.

Upon further consideration of general marketing issues related to female health care products it was determined that the prefix "ORTHO" should be added to this trademark. We have incorporated this prefix into other trademarks from our line of female health care products.

We hereby amend the original NDA 21-040 with the trademark "ORTHO-PREFEST™" to request a review of the trademark by the Division and the Labeling and Nomenclature Committee. We ask that the Division present this trademark to the Committee at the next scheduled meeting and to provide us with the decision of the Division and the LNC as soon as it is available.

If you have questions regarding this information please contact me at (908) 704-4469.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL

BC

ORIG AMENDMENT

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

JAN 2 0 1999

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

AMENDMENT TO A PENDING APPLICATION
Chemistry Information

Dear Dr. Rarick:

Reference is made to pending NDA 21-040 for ORTHO-PREFEST™ and to a request for this amendment from Dr. Ali Al-Hakim, Chemistry Reviewer, Division of Gastrointestinal and Coagulation Drug Products, FDA. Dr. Al-Hakim contacted The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) on January 13, 1999 noting that the study report TS-98011, entitled "The Physical-Chemical Characterization of Selected Properties of Norgestimate (RWJ-10131-000)", listed two suppliers for norgestimate drug substance: Dr. Al-Hakim also noted that the Drug Substance section of NDA Item 4 (Chemistry, Manufacturing and Controls) identifies only as the supplier of norgestimate drug substance. It was confirmed with him that RWJPRI intended to seek approval of only as the norgestimate drug substance supplier at this time. Dr. Al-Hakim requested that RWJPRI amend the NDA to clearly stipulate this confirmation.

Therefore, we hereby amend NDA 21-040 to declare that the original NDA, as submitted on December 23, 1998, provides for only one drug supplier of norgestimate drug substance: In the future, should RWJPRI seek approval of as an alternate supplier of norgestimate drug substance, we will submit to FDA the appropriate information necessary for a supplement to the application in accordance with 21 CFR 314.70.

If you have questions regarding this information please contact me at (908) 704-4469.

Sincerely,

Patricia M. Johnson
Principal Regulatory Affairs Scientist
Regulatory Affairs

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 2 1 1999
HFD-580

CC: Ali Al-Hakim, Ph.D., Chemistry Reviewer, HFD-180, Room 6B-45, Parklawn Building.

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

DEC 23 1998

Lisa Rarick, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-040/User Fee 3599
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

NEW DRUG APPLICATION

Dear Dr. Rarick:

Pursuant to the provisions of section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a New Drug Application for ORTHO-PREFEST™ Tablets (17β-estradiol and norgestimate). ORTHO-PREFEST™ is a unique combination estrogen/progestin hormone replacement therapy (HRT) regimen which is indicated for the treatment of moderate to severe vasomotor symptoms, treatment of vulvovaginal atrophy, and the prevention of osteoporosis. This combination estrogen/progestin HRT regimen provides protection from endometrial hyperplasia which can result from the use of estrogen replacement therapy. The following numbers were assigned to this application: NDA 21-040 and User Fee No. 3599. This application was prepared in accordance with 21 CFR 314.50 and applicable guidelines.

ORTHO-PREFEST™ consists of micronized 17β-estradiol (E2) as the estrogen and micronized norgestimate (NGM), as the progestin. ORTHO-PREFEST™ will be provided to the patient in a blister card containing 30 tablets which are taken once daily by mouth. The regimen has two oral tablets - one oral tablet of the regimen contains E2 and is round, pink, and debossed. The other is a combination tablet which is round, debossed, and white, and contains the two active ingredients E2 and NGM. The patient must take one tablet daily in the following sequence: One tablet containing E2 for three days, followed by one tablet containing E2 and NGM for the next three days. The sequence of the tablets is repeated for each 30 day treatment period.

CANDA/Electronic File Requirement

To satisfy FDA's requirement for submission of computer assisted NDA (CANDA) information, we are providing electronic files for the following NDA items:

Item 2: Overall NDA Summary
Item 3: Labels/Labeling

Item 4: Chemistry, Manufacturing and Controls
Item 5: Nonclinical Pharmacology and Toxicology
Item 6: Human Pharmacokinetics and Bioavailability
Item 8/10: Clinical and Statistical Data

The noted information is provided on one CD-ROM (WORD 7.0, PDF, SAS, or ASCII files) (Attachment 1). FDA's "Draft Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs" (April 1998) was consulted in the preparation of the CD-ROM provided. The CD-ROM is located in the **Archival Copy** of the first volume of the NDA (NDA Volume 1.001). This CD-ROM may be loaded onto the Division's network as is; an index of the contents of the CD-ROM is also provided in NDA Volume 1.001. We assure the Division that the programs provided have been appropriately scanned using the McAfee Vshield program, version 4.0.1 and are virus-free.

FDA Agreements

The following major agreements were reached at the Pre-NDA Meeting held March 31, 1998 with members of the Division of Reproductive and Urologic Drug Products and RWJPRI (Attachment 2):

- RWJPRI can submit additional drug product stability data after submission of the NDA (not later than 6 months after submission of the NDA).
- Cross-reference to the approved NDAs for ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® (NDAs 19-653 and 19-697, respectively) may be made for previously submitted reports and information relevant to CMC, Nonclinical Pharmacology and Toxicology, and Human Pharmacokinetics with respect to norgestimate and progestins.
- The clinical and non-clinical programs were considered sufficient to support the regimen that is the subject of this application for review. No additional studies were requested.
- Tabulations (NDA Item 11) are routinely provided as appendices to RWJPRI's clinical study reports. Therefore, the requirement for NDA Item 11 (Tabulations) is satisfied with the submission of the full study reports in NDA Item 8 (Clinical Data).

Agreements reached during post-meeting communications between the Division and RWJPRI are also appended as attachments to the cover letter (Attachment 3). The following are a few of the major post-meeting agreements:

- The study report for the two Phase 3 studies ESTNRG-CHRT-102 and ESTNRG-CHRT-103 may be combined into one report. Data listings for the two individual studies, however, should remain separate by investigator and study.
- The requirement for submission of Item 10 (Statistical Section) can satisfied with the submission of one additional copy of the appropriate volumes of Item 8 (Clinical Data section - Overall NDA volumes 1.047 and 1.061 to 1.229), as noted in FDA's Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications (July 1988). These volumes will be

submitted in the green Statistical jackets. Please note that the Archival copy of the NDA will only reflect submission of Item 8.

Demonstration of Safety and Efficacy

Pursuant to 505(b)(1) of the Act, the safety and efficacy of ORTHO-PREFEST™ in the treatment of moderate to severe vasomotor symptoms, treatment of vulvovaginal atrophy and prevention of estrogen-dependent endometrial hyperplasia was established in thirteen clinical studies conducted by RWJPRI and our worldwide affiliates. This clinical program included seven Phase 1 and six Phase 2/Phase 3 studies to provide exposure to ORTHO-PREFEST™ in over 3000 women.

By confirmation with the Division on November 19, 1998, the indication for prevention of osteoporosis is being submitted with this NDA in the form of a FD&C Act 505(b)(2) application. (Attachment 4) The clinical section (NDA Item 8) includes a justification for granting the claim of osteoporosis prevention to the ORTHO-PREFEST™ HRT regimen. This justification is supported by relevant data from the published literature regarding the use of estradiol for prevention of osteoporosis as well as unpublished data from clinical trials utilizing estrogens. RWJPRI has also included the full study reports from two clinical studies which established the bioequivalence of our E2 tablets with the reference listed drug product, Estrace® (estradiol tablets, USP), manufactured by . These study reports are provided in Item 6 of the NDA as requested by Dr. Parekh on November 19, 1998. The "Request for Waiver" for the 1 mg E2 tablet and comparative dissolution data for RWJPRI's E2 tablets and Estrace® are also provided in Item 6 of the NDA.

Physician's Package Insert/Patient Instructions

The draft Physician's Package Insert and Patient Instructions were prepared in accordance with 21 CFR 314.50 (and 310.56) and applicable guidelines including: the Guidance for Progestin Class Labeling (December 1988) and the Draft Guidance for Industry on Non-Contraceptive Estrogen Class Labeling (Federal Register October 15, 1998). It was confirmed by teleconference with Ms. Diane Moore, CSO on November 19, 1998 that RWJPRI should prepare the noted labeling in accordance with the draft guidance since it reflects the Division's current thinking on the subject.

Child-Resistant Closure

On November 4, 1998, the U.S. Consumer Product Safety Commission (CPSC) granted RWJPRI a stay from enforcement from the Poison Prevention Packaging Act (PPPA), 15 USC 1471-1476, and its accompanying regulations. (Attachment 5)

Trademark

Our trademark was submitted to the Division on May 18, 1998 to IND and deemed "acceptable" by FDA's Labeling and Nomenclature Committee. This agreement was confirmed by facsimile transmission on June 23, 1998. (Attachment 6)

Reviewer's Guides

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

21 CFR 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)

Desk Copies

As requested by Ms. Diane Moore, CSO, a desk copy of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) is provided. The desk copies of the ISS and ISE are bound in black paperboard jackets and are addressed to the attention of Ms. Moore. We are also providing Ms. Moore with a desk copy of NDA volumes 1.001 and 1.002.

User Fee

The required User Fee of was submitted under separate cover to Mellon Bank, Pittsburgh, PA on December 11, 1998 (User Fee No. 3599). The required User Fee Cover Sheet (Form FDA 3397) is signed and included in this application.

Should you have questions concerning this application, please contact Patricia Johnson at (908) 704-4469, or our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

David Goldberger, R.Ph., M.S.
Assistant Director
Regulatory Affairs

Patricia M. Johnson
Principal RA Scientist
Regulatory Affairs

Enclosures

CC: Ms. Diane Moore, CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

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

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

FOR FDA USE ONLY

APPLICATION NUMBER
21040

APPLICANT INFORMATION

NAME OF APPLICANT
The R.W. Johnson Pharmaceutical Research Institute

DATE OF SUBMISSION
DEC 23 1998

TELEPHONE NO. (*Include Area Code*)
(908) 704-4022

FACSIMILE (FAX) Number (*Include Area Code*)
(908) 722-5113

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 21-040

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
17β-estradiol and norgestimate

PROPRIETARY NAME (*trade name*) IF ANY
ORTHO-PREFEST™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*)

DOSAGE FORM: tablet

STRENGTHS: 1mg estradiol tablet and 1mg estradiol/0.90mg norgestimate tablet

ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate to severe vasomotor symptoms, vulvovaginal atrophy and prevention of osteoporosis

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) ☐ 507

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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Request for marketing authorization

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

NUMBER OF VOLUMES SUBMITTED 288

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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.

Refer to Item 4A Chemistry, Manufacturing and Controls (NDA Volumes 1.004 to 1.008)

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

IND NDA 19-697; NDA 19-653
DMF DMF DMF DMF DMF DMF

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 24 1998
CDR

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 29 1998
HFD-580

FORM FDA 356h (7/97)

This application contains the following items: (*Check all that apply*)	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	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)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	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))
X	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)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
X	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)
X	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. 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
David Goldberger	**David Goldberger, RPh, MS** **Assistant Director, Regulatory Affairs**	DEC 23 1998

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 **Raritan, New Jersey 08869-0602**	**(908) 704-4022**

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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

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

DEC 11 1998

Mellon Bank
525 William Penn Way
Three Mellon Center
27th Floor (FDA 360909) Room 153-2713
Pittsburgh, PA 15259-0001

NDA 21-040
ORTHO-PREFEST™ Tablets
(17β-estradiol and norgestimate)

USER FEE NO. 3599

Dear Sir/Madam:

Enclosed please find a company check in the amount of to cover User Fee expenses for ORTHO-PREFEST™ (17β-estradiol and norgestimate) Tablets NDA 21-040. ORTHO-PREFEST™ is indicated for the treatment of moderate to severe vasomotor symptoms attributed to the menopause, vulvovaginal atrophy, prevention of osteoporosis and protection from estrogen-induced endometrial hyperplasia. A completed unsigned User Fee Cover Sheet (Form FDA 3397) is also enclosed. The signed and dated User Fee Cover Sheet will accompany the original NDA submission.

If you have questions regarding this information, please contact me at (908) 704-4469, or our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Patricia M. Johnson
Principal RA Scientist
Regulatory Affairs

Enclosures

cc: Diane Moore, CSO (FDA/CDER HFD-580)

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LA JOLLA RARITAN SPRING HOUSE