

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-241

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-241</u> /S- _____ - _____	
Drug <u>ORTHO TRI-CYCLEN Lo</u> (norgestimate/ethinyl estradiol) Tablets	Applicant <u>Johnson & Johnson Pharmaceutical Research</u>
RPM <u>Jennifer Mercier</u>	Phone <u>301-827-4260</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3S</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>August 25, 2002</u> Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling?	Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels	X
Nomenclature review	X

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.

Exception for review (Center Director's memo).....	N/A
OC Clearance for approval.....	N/A

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	X Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Copy of Press Release or Talk Paper.....	N/A
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	X
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	X
Disclosable information – indicate where review is located	X
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting <u>1/8/97</u>	
Date of pre NDA Meeting <u>10/4/99 & 6/22/99 & 10/29/97</u>	
Date of pre-AP Safety Conference <u>N/A</u>	
◆ Advisory Committee Meeting	N/A
Date of Meeting	N/A
Questions considered by the committee	N/A
Minutes or 48-hour alert or pertinent section of transcript	N/A
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	X
◆ Clinical review(s) and memoranda	X

◆ Safety Update review(s)	<u> X </u>
◆ Pediatric Information	<u> X </u>
X Waiver/partial waiver (Indicate location of rationale for waiver) <input type="checkbox"/> Deferred Pediatric Page.....	<u> X </u>
<input type="checkbox"/> Pediatric Exclusivity requested? <input type="checkbox"/> Denied <input type="checkbox"/> Granted X Not Applicable	
◆ Statistical review(s) and memoranda	<u> X </u>
◆ Biopharmaceutical review(s) and memoranda.....	<u> X </u>
◆ Abuse Liability review(s)	<u> N/A </u>
Recommendation for scheduling	<u> N/A </u>
◆ Microbiology (efficacy) review(s) and memoranda	<u> N/A </u>
◆ DSI Audits	<u> N/A </u>
<input type="checkbox"/> Clinical studies <input type="checkbox"/> bioequivalence studies	<u> N/A </u>

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

◆ CMC review(s) and memoranda	<u> X </u>
◆ Statistics review(s) and memoranda regarding dissolution and/or stability	<u> N/A </u>
◆ DMF review(s)	<u> X </u>
◆ Environmental Assessment review/FONSI/Categorical exemption	<u> X </u>
◆ Micro (validation of sterilization) review(s) and memoranda	<u> N/A </u>
◆ Facilities Inspection (include EES report)	<u> X </u>
Date completed _____	X Acceptable <input type="checkbox"/> Not Acceptable
◆ Methods Validation	<input type="checkbox"/> Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

◆ Pharm/Tox review(s) and memoranda	<u> X </u>
◆ Memo from DSI regarding GLP inspection (if any)	<u> N/A </u>

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

**APPEARS THIS WAY
ON ORIGINAL**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-241</u> /SE _____ - _____	
Drug <u>ORTHO TRI-CYCLEN™ Lo</u> (noregestimate/ethinyl estradiol)	Applicant <u>R.W. Johnson Pharmaceutical Research Institute</u>
RPM <u>Jennifer Mercier</u>	Phone <u>301-827-4260</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>11,391</u>	
Application classifications: Chem Class <u>3S</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>June 25, 2001</u> Secondary <u>August 25, 2001</u>

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling?	X Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels	X
Nomenclature review	X

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.

Exception for review (Center Director's memo).....	N/A
OC Clearance for approval.....	N/A

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	X Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	N/A
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Copy of Press Release or Talk Paper.....	N/A
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	X
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	X
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	X
Disclosable information – indicate where review is located	N/A
.....	X
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting <u>1/8/97</u>	
Date of pre NDA Meeting <u>10/4/99 & 6/22/99 & 10/29/97</u>	
Date of pre-AP Safety Conference <u>N/A</u>	
◆ Advisory Committee Meeting	N/A
Date of Meeting	N/A
Questions considered by the committee	N/A
Minutes or 48-hour alert or pertinent section of transcript	N/A
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	6-25-01
◆ Clinical review(s) and memoranda	6-25-01

◆ Safety Update review(s)	<u>6-25-01</u>
◆ Pediatric Information	X
X Waiver/partial waiver (Indicate location of rationale for waiver) <input type="checkbox"/> Deferred Pediatric Page.....	<u>X</u>
<input type="checkbox"/> Pediatric Exclusivity requested? <input type="checkbox"/> Denied <input type="checkbox"/> Granted X Not Applicable	
◆ Statistical review(s) and memoranda	<u>6-22-01</u>
◆ Biopharmaceutical review(s) and memoranda.....	<u>6-25-01</u>
◆ Abuse Liability review(s)	N/A
Recommendation for scheduling	<u>N/A</u>
◆ Microbiology (efficacy) review(s) and memoranda	<u>N/A</u>
◆ DSI Audits	N/A
<input type="checkbox"/> Clinical studies <input type="checkbox"/> bioequivalence studies	<u>N/A</u>

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

◆ CMC review(s) and memoranda	<u>6-21-01</u>
◆ Statistics review(s) and memoranda regarding dissolution and/or stability	<u>N/A</u>
◆ DMF review(s)	<u>X</u>
◆ Environmental Assessment review/FONSI/Categorical exemption	<u>X</u>
◆ Micro (validation of sterilization) review(s) and memoranda	<u>N/A</u>
◆ Facilities Inspection (include EES report)	X
Date completed <u>6-21-01</u>	X Acceptable <input type="checkbox"/> Not Acceptable
◆ Methods Validation	<input type="checkbox"/> Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

◆ Pharm/Tox review(s) and memoranda	<u>3-27-01</u>
◆ Memo from DSI regarding GLP inspection (if any)	<u>N/A</u>

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

**APPEARS THIS WAY
ON ORIGINAL**

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>The R.W. Johnson Pharmaceutical Research Institute 920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602</p>	<p>3. PRODUCT NAME</p> <p><u>norgestimate/ethinyl estradiol</u></p> <p>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(908) 704-4812</p>	<p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 21-241</p>
<p>5. USER FEE I.D. NUMBER</p> <p>3906</p>	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 <i>(Self Explanatory)</i>	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY <i>(Self Explanatory)</i>	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(see reverse if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes 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 (0910-0297)
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.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p>Ramon Polo, PhD</p>	<p>TITLE</p> <p>Director, Regulatory Affairs</p>	<p>DATE</p> <p>AUG 25 2000</p>
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(F)

**Number of Pages
Redacted** 94



Draft Labeling
(not releasable)

(F)

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Foreign Labeling
N/A

ISI
8/21/02

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

**ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol**

R.W. Johnson Research Pharmaceutical Institute

3S

**PM: Jennifer Mercier
HFD-580
7-4260**

Foreign Labeling

N/A

**ISI
6/14/01**

**APPEARS THIS WAY
ON ORIGINAL**

Ⓞ

**Number of Pages
Redacted** (58 + 266) =

324 pages



Draft Labeling
(not releasable)

Ⓞ

(H)

Number of Pages
Redacted 20



Draft Labeling
(not releasable)

(H)

Memo

To: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Nora Roselle, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support (DMETS)
HFD-420

Through: Alina Mahmud, RPh
Team Leader, Division of Medication Errors and Technical Support (DMETS)
HFD-420

Jerry Phillips, RPh
Associate Director, Office of Drug Safety

CC: Jennifer Mercier
Project Manager, HFD-580

Date: August 16, 2002

Re: ODS Consult 01-0053-1; Ortho Tri-Cyclen Lo
(Norgestimate and Ethinyl Estradiol Tablets, USP)
0.180 mg/0.025 mg, 0.215 mg/0.025 mg, 0.250 mg/0.025 mg; NDA 21-241

This memorandum is in response to a July 25, 2002, request from your Division for a re-review of the proprietary name, Ortho Tri-Cyclen Lo. The proposed proprietary name, Ortho Tri-Cyclen Lo, was found unacceptable by DMETS in the initial name review on March 15, 2001 (ODS Consult 01-0053).

DMETS originally reviewed the proprietary name _____ and did not recommend the proposed name on December 12, 2000. The sponsor submitted another proprietary name, "Ortho Tri-Cyclen Lo". The following information was taken from ODS Consult 01-0053:

**APPEARS THIS WAY
ON ORIGINAL**

The proprietary name, Ortho Tri-Cyclen, is currently available as Ortho Tri-Cyclen 21 tablets and Ortho Tri-Cyclen 28 tablets. Ortho Tri-Cyclen is a triphasic combination oral contraceptive containing two active ingredients, ethinyl estradiol (0.035 mg) and norgestimate (0.18 mg, 0.215 mg, and 0.250 mg). The proposed product, Ortho Tri-Cyclen Lo, will contain 0.025 mg of ethinyl estradiol instead of 0.035 mg, which is contained in the currently marketed product. Currently in the U.S. market, the proprietary names Lo-Ovral and Ovral are available. Ovral contains 0.5 mg of norgestrel and 0.05 mg of ethinyl estradiol. Lo-Ovral contains a lower amount of norgestrel (0.3 mg) and ethinyl estradiol (0.03 mg) than Ovral. Hence, "Lo" is placed in front of the proprietary name, Ovral, to differentiate one product from another.

In regard to the proposed name, Ortho Tri-Cyclen Lo, we recognize that the suffix, "Lo", is used to distinguish the proposed product from the currently marketed product, Ortho Tri-Cyclen. The "Lo" is appropriate since the proposed product contains a lower amount of ethinyl estradiol than the currently available product, Ortho Tri-Cyclen. However, we recommend placing "Lo" in front of the name, "Ortho Tri-Cyclen," for two reasons. First, prescribers may forget to write "Lo" when ordering this proposed product if "Lo" is at the end of the name, then the patients could receive the currently available product instead. Second, the proposed product, ~~Ortho Tri-Cyclen Lo~~ would most likely be stored separately from Ortho Tri-Cyclen on pharmacy shelves and prevent dispensing errors. Consequently, DMETS recommends ~~Ortho Tri-Cyclen Lo~~

Furthermore, one additional concern regarding the tradename "Ortho Tri-Cyclen Lo" was identified during final review discussions. DMETS believes that prescriptions written for "Ortho Tri-Cyclen Lo"

Ortho tri-cyclen lo # 1

may be misinterpreted as "Ortho Tri-Cyclen PO" meaning "Ortho Tri-Cyclen by mouth". In this case, the patient could receive the currently available product instead of the intended lower strength formulation.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Ortho Tri-Cyclen Lo since we conducted our initial review on March 15, 2001 (ODS Consult 01-0053) that would render the name objectionable. However, DMETS recommends the use of ~~Ortho Tri-Cyclen Lo~~ as stated in our previous tradename review.

DMETS recommended labeling revisions to minimize potential errors; please refer to ODS Consult #00-0209.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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

/s/

Nora L. Roselle
8/16/02 02:56:59 PM
CSO

Alina Mahmud
8/16/02 03:15:41 PM
PHARMACIST

Jerry Phillips
8/16/02 03:22:44 PM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**



Memorandum

Date: March 15, 2001

From: OPDRA, Medication Error Prevention, HFD-400

Through: Jennifer Mercier, Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

Subject: Ortho Tri-Cyclen Lo
R.W. Johnson Pharmaceutical Research Institute
NDA 21-241
Consult #01-0053

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

OPDRA has reviewed the proprietary name "Ortho Tri-Cyclen Lo", and we recommend _____ instead.

OPDRA originally reviewed the proprietary name _____ and we did not recommend the proposed name on December 12, 2000. The sponsor has submitted another proprietary name, "*Ortho Tri-Cyclen Lo*." The proprietary name, Ortho Tri-Cyclen, is currently available as Ortho Tri-Cyclen 21 tablets and Ortho Tri-Cyclen 28 tablets. This product is a triphasic combination oral contraceptive containing two active ingredients, ethinyl estradiol (0.035 mg) and norgestimate (0.18 mg, 0.215 mg, and 0.250 mg). The proposed product, *Ortho Tri-Cyclen Lo*, will contain 0.025 mg of ethinyl estradiol instead of 0.035 mg, which is contained in the currently marketed product.

In current U.S. market, the proprietary names, Lo-Ovral and Ovral, are available. Ovral contains 0.5 mg of norgestrel and 0.05 mg of ethinyl estradiol. Lo-Ovral contains a lower amount of norgestrel (0.3 mg) and ethinyl estradiol (0.03 mg) than Ovral. Hence, "Lo" is placed in front of the proprietary name, Ovral, to differentiate one product from another. In regard to the proposed name, *Ortho Tri-Cyclen Lo*, we recognize that the suffix, "Lo", is used to distinguish the proposed product from the currently marketed product, Ortho Tri-Cyclen. The "Lo" is appropriate since the proposed product contains a lower amount of ethinyl estradiol than the currently available product, Ortho Tri-Cyclen. However, we recommend placing "Lo" in front of the name, "Ortho Tri-Cyclen," for two reasons. First, prescribers may forget to write "Lo" when ordering this proposed product if "Lo" is at the end of the name, then the patients could receive the currently available product instead. Second, the proposed product, _____ would most likely be stored separately from Ortho Tri-Cyclen on pharmacy shelves and prevent dispensing errors. Consequently, OPDRA recommends _____

OPDRA recommended labeling revisions to minimize potential errors; please refer to consult #00-0209.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised

labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

Hye-Joo, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Hye-Joo Kim
3/16/01 08:39:01 AM
PHARMACIST

Jerry Phillips
3/16/01 08:48:33 AM
DIRECTOR

Martin Himmel
3/19/01 01:09:02 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: January 31, 2001

DUE DATE: March 30, 2001

OPDRA CONSULT #: 00-0209-2

TO: Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Jennifer Mercier, Project Manager
HFD-580

PRODUCT NAME:

(Norgestimate and Ethinyl Estradiol
tablets, USP)

APPLICANT: R.W. Johnson Pharmaceutical Research Institute

MANUFACTURER: Ortho-McNeil Pharmaceutical, Inc.

NDA #: 21-241

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary names '_____' to determine the potential for confusion with approved proprietary and generic names as well as pending names. We did not recommend the use of the proprietary name on December 12, 2000. OPDRA's review was forwarded to the sponsor for review and comment. The sponsor responded on January 26, 2001. The sponsor submitted a list of actions they performed to address our concerns that were raised earlier. First, they discontinued all Ortho McNeil 21-day oral contraceptives. Second, they sent letters to health care professionals not to write "21" or "28" when ordering oral contraceptives, because 21 day regimens are no longer available. OPDRA reviewed the actions performed by the sponsor and concluded that actions taken by the sponsor were not persuasive to minimize the Agency's concern with regard to potential medication errors due to name confusion.

OPDRA RECOMMENDATION: After review of the information submitted by the sponsor, OPDRA does not recommend the use of the proprietary name '_____'

**APPEARS THIS WAY
ON ORIGINAL**

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 14, 2001
NDA NUMBER: 21-241
NAME OF DRUG: _____
(Norgestimate and Ethinyl Estradiol tablets, USP)
NDA HOLDER: R.W. Johnson Pharmaceutical Research

I. INTRODUCTION

This consult was written in response to a request from the sponsor for the Agency to reconsider the acceptability of the proprietary name, _____

The sponsor originally submitted the proposed proprietary name, _____, under IND 11-391, and the CDER Labeling and Nomenclature Committee (LNC) accepted it on February 9, 1999. However, on April 10, 2000, the sponsor requested to change the proposed proprietary name from _____ "upon further consideration of general marketing issues related to female health care products."

OPDRA completed a Proprietary Name Review for this product on December 12, 2000 and did not recommend the use of the name, _____. In response to OPDRA's December 12, 2000 concerns regarding the unacceptability of the proprietary name, the sponsor took the following steps in an effort to prevent potential medication and dispensing errors associated with dispensing _____

- Discontinued all 21-day put-ups throughout the entire Ortho McNeil brands to prevent potential confusion relating to _____
- Explained that the proprietary name, _____, most accurately describes the product, because "Tri" describes the triphasic regimen and "Cyclen" describes the progestin component.
- Disseminated letters to inform health care professionals about the discontinuation of the 21-day regimen and to "instruct health care providers that they do not need to indicate "21" or "28" on their prescriptions for oral contraceptives."
- The sponsor has substantive plans to educate pharmacists and health care providers about _____

PRODUCT INFORMATION

_____ contains 0.025 mg of ethinyl estradiol instead of 0.035 mg, which is contained in the currently marketed products. _____ is indicated for prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Combination oral contraceptives prevent pregnancy by suppression of gonadotropins and the primary mechanism of this action is inhibition of ovulation. Unlike the currently marketed products, Ortho Tri-Cyclen 21 and 28 tablets, the proposed product: _____
_____ The recommended dose is one tablet daily. _____ is supplied in a DIALPAK Tablet dispenser or in a VERIDATE Tablet dispenser (for clinic usage), and each dispenser contains 28 tablets as follows:

- 7 white tablets contain 0.180 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 light blue tablets contain 0.215 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 dark blue tablets contain 0.250 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 green tablets contain inert ingredients.

II. RISK ASSESSMENT

OPDRA's original consult addressed concerns of the modifier, _____ because the modifier could be mistaken as: _____ of the same ingredients and strengths as the currently marketed products, Ortho Tri-Cyclen 21 and 28. We also raised the issue that the modifier, _____, only reflects one of the two active ingredients, ethinyl estradiol. Finally, we were concerned that the modifier, _____ could be misinterpreted as "28" when scripted and patients could receive the unintended products. The sponsor states that they anticipated the potential confusion over the use of _____ in the trademark too. The sponsor submitted a list of actions they performed to address our concerns that were raised earlier and this information is summarized below:

A. *SPONSOR'S COMMENT TO OPDRA'S OBJECTION TO THE MODIFIER, _____ BECAUSE IT MAY BE MISTAKEN FOR _____ DAY REGIMEN.*

As a therapeutic class, 98.5% of all oral contraceptive prescriptions are dispensed as 28-day regimens; 21-day regimens represent even less than 1.5% of all cycles dispensed in the Ortho-McNeil product line. Nonetheless, we also anticipated the potential for confusion over the use of _____ in the trademark, since both 21- and 28-day regimens exist. Thus, as a company, we elected to discontinue all 21-day put-ups throughout our entire oral contraceptive line. We have informed health care providers, pharmacists, and the trade of this decision. We have also instructed health care providers that they do not need to indicate "28" on their prescriptions for OCs, as well. This communication occurred via letter and through our field sales force.

Currently, the Ortho Tri-Cyclen line consists of only 28-day packs. If approved, Ortho _____ would also consist of 28-day packs only. The potential for either dispensing errors or dosing errors arising from ambiguity around the number of days in a cycle of OCs should be negligible now that all of our OC products will reflect the same, 28-day dosing regimen. (...preliminary mock-up of _____)

Dialpaks, which illustrate clear denotation of the 28-day regimen in plain sight of the trademark itself.) We believe that this action effectively addresses OPDRA's concern over potential confusion among our consumers, physicians, and pharmacists.

OPDRA'S COMMENT:

In response to OPDRA's concern about potential confusion between the proposed product, _____ and the currently marketed products, **Ortho Tri-Cyclen 21 and 28**, the sponsor stopped manufacturing all 21-day regimens for all Ortho McNeil oral contraceptives. Now, Ortho Tri-Cyclen line consists of only 28-day. In addition, due to the discontinuation of 21-day regimen, prescribers are now instructed by the sponsor not to write 21 or 28 with the proprietary name, **Ortho Tri-Cyclen**.

According to the sponsor, with the deletion of 21-day regimens, **Ortho Tri-Cyclen** without the modifier will be clear to the providers that **Ortho Tri-Cyclen** is the currently available product which contains norgestimate (0.18 mg, 0.215 mg, and 0.25 mg) and ethinyl estradiol (0.35 mg). Hence, the proposed product, _____, will be clear to health professionals that it contains the same amount of norgestimate, but a different amount of ethinyl estradiol: 25 mcg of ethinyl estradiol.

OPDRA does not agree with the sponsor that the discontinuation of 21-day regimens will prevent potential confusion between the proposed product, _____ and the currently available product, **Ortho Tri-Cyclen**, for the following reasons:

The health professionals have been familiar with the fact that the modifiers that follow the proprietary name, **Ortho Tri-Cyclen**, represent "day regimens" since the introduction of **Ortho Tri-Cyclen** in the United States market on July 3, 1992. Hence, the sudden discontinuation of **Ortho Tri-Cyclen** 21-day regimen is not going to change nine years of commonly held knowledge that the modifiers that follow **Ortho Tri-Cyclen** represent "day regimens," even with the extensive educational campaigns targeted to health professionals. Many health professionals will continue to prescribe the currently available product as "**Ortho Tri-Cyclen 28**" with or without the availability of **Ortho Tri-Cyclen 21**.

Ortho McNeil may have discontinued their product lines that contain 21-day regimens, however, other manufacturers still provide 21 day regimens. In the current market place, health care professionals and consumers understand that the modifiers used in conjunction with the oral contraceptive trade names are often used to denote the day regimens. Hence, many providers could interpret _____ as _____-tablets" of the currently available product, **Ortho Tri-Cyclen** despite the discontinuation of 21-day regimens by Ortho McNeil.

OPDRA disagrees with the sponsor that "the potential for either dispensing errors or dosing errors arising from ambiguity around the number of days in a cycle of OCs should be negligible," because all of the sponsor's OC products will now only reflect 28-day dosing regimen for the following reason:

Providers usually prescribe **Ortho Tri-Cyclen** without the modifiers, 21 or 28, because the substitution of 21-day regimen for 28-day regimen or vice versa does not result in treatment failures. Often patients themselves decide to take either 21-day or 28-day regimens. If the proposed product is approved, it is expected that when **Ortho Tri-Cyclen** is prescribed, the pharmacist will dispense the currently available product without asking the patient. Consequently, if a provider inadvertently forgets to write the intended modifier, _____ on a prescription, then the patient will receive the currently available product, **Ortho Tri-Cyclen**, and ingest the incorrect amount of ethinyl estradiol. Furthermore, patients may be unable to discover this error, because _____ and **Ortho Tri-Cyclen** will be dispensed in the same color diskpaks containing the same color tablets.

We disagree with the sponsor that the sudden discontinuation of 21-day regimens will make it clear to health professionals that _____ contains a different amount of ethinyl estradiol than **Ortho Tri-Cyclen**. Although the modifier, _____ may have been intended to denote 25 micrograms of ethinyl estradiol, this implication is not obvious due to the possible misinterpretation of the modifier, "_____." Also, the currently marketed proprietary name, **Ortho Tri-Cyclen**, does not express the strength of ethinyl estradiol, so it is not clear what the modifier, _____ represents something other than the day regimen.

The sponsor submitted a container label of **Ortho Tri-Cyclen** and a preliminary label mock-up of _____ Dialpaks, which illustrates clear denotation of the 28-day regimen in plain sight of the trademark itself. This clear denotation of the 28-day regimen may help the pharmacist choose the correct product when dispensing, but this does not assist prescribers in readily distinguishing one product from another nor writing intended prescriptions clearly. In turn, pharmacists may incorrectly interpret the intention of the prescribers.

B. SPONSOR'S COMMENT TO OPDRA'S OBJECTION TO THE USE OF _____ BECAUSE IT ONLY REFLECTS ONE OF THE TWO ACTIVE INGREDIENTS.

We believe that _____ is the name that most accurately describes the product. The type, dose, and triphasic regimen of the progestin component is identical to our currently marketed **Ortho Tri-Cyclen**. In fact, the foundation of the name of our new product accurately describes the regimen: "Tri" describes the triphasic regimen and "Cyclen" describes the progestin component. Taken together, the name connotes the widely held knowledge that the progestin dose given is 180-215-250 mcg, each given for 7 days. All "Cyclen" OCs contain norgestimate, just as all "Ortho Novum" OCs contain norethindrone. Physicians have clearly indicated to us their expectations that new drugs within an OC product line containing the same progestin would bear the same root name as the original OC.

Additionally, there are other products that have numerical suffices that only describe the estrogen component: **OVCON 35** and **OVCON 50** as an example. We have substantive plans to educate pharmacists and health care providers about this product. The logo would clearly indicate "28 day regimen." We believe that these

observations speak directly to the second concern raised by OPDRA, namely, that the numerical suffix refers only to the estrogen component of the product.

OPDRA's RESPONSE:

According to the sponsor, the currently available name, **Ortho Tri-Cyclen**, represents the following: "Tri" represents the triphasic regimen, and "Cyclen" describes the progestin component, 180-215-250 micrograms of norgestimate. According to the sponsor, "physicians have clearly indicated" to them that "their expectation that new drugs within an OC product line containing the same progestin would bear the same root name as the original OC."

OPDRA's concern is not with the root name Ortho Tri-Cyclen. We objected to the modifier, — because the modifier, — is misleading and not useful in differentiating the proposed product from the currently available product, Ortho Tri-Cyclen for the following reasons:

The proposed name, (— express the strength of ethinyl estradiol, — micrograms, but the name **Ortho Tri-Cyclen** does not represent 35 micrograms of ethinyl estradiol. Although the modifier, — may have been intended to denote 25 micrograms of ethinyl estradiol, this implication is not obvious due to the lack of representation of the strength of ethinyl estradiol in the proprietary name, **Ortho Tri-Cyclen**. In addition, the modifier, — could be misinterpreted as — tablets of the same active ingredients and strengths as the currently marketed product, **Ortho Tri-Cyclen**.

There are multitudes of oral contraceptive brands and it is unlikely that many providers know neither the active ingredients nor their strengths of the majority of these products. Hence, the providers recognize oral contraceptives by the proprietary names. The proprietary names should clearly distinguish one OC from another within the same manufacturer, especially if two products contain the same active ingredients as in Ovcon 35 and Ovcon 50.

We also acknowledge that the proprietary names, OVCON 35 and 50, express only the estrogenic component. However, the proprietary names, Ovcon 35 and Ovcon 50, use the modifiers to differentiate one product from another. The modifier, "35", is used to express 35 micrograms of ethinyl estradiol contained in Ovcon 35 and the modifier, "50", expresses 50 micrograms of ethinyl estradiol contained in Ovcon 50. If the sponsor uses this argument, Ortho Tri-Cyclen that contains 35 micrograms of ethinyl estradiol should have been named as follows: Ortho Tri-Cyclen 35. Then the proposed name, — would have been appropriate since the — would have represented — micrograms contained in the proposed product and would have differentiated it from the currently available product.

The sponsor plans to extensively educate pharmacists and health care providers about (— OPDRA believes that our pre-marketing evaluations and risk analysis is the best preventative tool in reducing medication errors related

to similar names. The proposed educational campaign is directed at increasing the awareness of health care practitioners to the possibility of medication errors involved with prescribing and dispensing _____ There is no scientific evidence that an increase in awareness by itself will prevent errors.

C. *ISSUES NOT ADDRESSED BY THE SPONSOR*

In our previous review, OPDRA addressed the potential medication errors that may occur with the modifier —. The modifier, — could look very similar to the modifier, “28,” or vice versa when scripted as demonstrated in the following written sample of prescription:

<i>Ortho Tri-Cylen —</i>	<i>Ortho Tri-Cylen 28</i>
--------------------------	---------------------------

_____ could be misinterpreted as **Ortho Tri-Cylen 28** when written; patients could receive the wrong oral contraceptive product. These products can not be substituted for one another. If a prescriber chooses to write “28” for the number of days of therapy, a pharmacist could mistakenly interpret it as — and thus dispense the incorrect product, _____

III. **RECOMMENDATIONS**

The applicant has failed to provide persuasive data or evidence to minimize the Agency’s concern with regard to potential medication errors between the proposed product, _____ and the currently marketed product, **Ortho Tri-Cylen**. Based on the lack of supportive data, OPDRA does not recommend the use of the proprietary name _____

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Hye-Joo Kim
2/26/01 10:11:57 AM
PHARMACIST

Jerry Phillips
2/26/01 10:15:47 AM
DIRECTOR

nulldate
DIRECTOR

Martin Himmel
2/28/01 11:19:36 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 11/02/2000

DUE DATE: 2/01/2001

OPDRA CONSULT #: 00-0209

TO: Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

THROUGH: Jennifer Mercier
Project Manager
(HFD-580)

PRODUCT NAME:

(Norgestimate and Ethinyl Estradiol tablets,
USP)

APPLICANT: R. W. Johnson Pharmaceutical Research Institute

MANUFACTURER: Ortho-McNeil Pharmaceutical Inc.

NDA #: 21-241

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-30), OPDRA conducted a review of the proposed proprietary name, _____ Ortho Tri-Cyclen is currently available as Ortho Tri-Cyclen 21 tablets and Ortho Tri-Cyclen 28 tablets.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proposed name, Ortho Tri-Cyclen 25. We also have made a number of recommendations for labeling revisions to minimize potential medication errors with the use of this product. See review for details.

/S/

1/2/01

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

1/10/01

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**APPEARS THIS WAY
ON ORIGINAL**

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 12, 2000
NDA NUMBER: 21-241
NAME OF DRUG: _____ (Norgestimate and Ethinyl Estradiol tablets)
NDA HOLDER: R.W. Johnson Pharmaceutical Research

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products to review the proprietary name, _____ regarding potential name confusion with other proprietary/generic drug names. In addition, the paperboard packer, pill pouch, blister pack, and the package insert were reviewed for possible interventions in minimizing medication errors.

The sponsor originally submitted the proposed trade name, _____ under IND 11-391, and it was accepted by the CDER Labeling and Nomenclature Committee (LNC) on February 9, 1999. However, on April 10, 2000, the sponsor requested to change the proposed name from _____ 'upon further consideration of general marketing issues related to female health care products.'

The proprietary name, Ortho Tri-Cyclen, is currently available as Ortho Tri-Cyclen 21 tablets and Ortho Tri-Cyclen 28 tablets. Ortho Tri-Cyclen was approved for the prevention of pregnancy on July 3, 1992 under NDA 19-697. Ortho Tri-Cyclen 21 and 28 are also indicated for the treatment of moderate acne vulgaris in females, ≥ 15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medication. This indication was approved on December 31, 1996 under NDA 20-681. This product is a triphasic combination oral contraceptive containing two active ingredients, ethinyl estradiol (0.035 mg) and norgestimate (0.18 mg, 0.215 mg, and 0.250 mg).

The sponsor, R.W. Johnson Pharmaceutical Research, has submitted this new application, NDA 21-241, for the same active ingredients. However, the proposed product will contain 0.025 mg of ethinyl estradiol instead of 0.035 mg which is contained in the currently marketed products. _____ is indicated for prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Combination oral contraceptives prevent pregnancy by suppression of gonadotropins and the primary mechanism of this action is inhibition of ovulation. Unlike the currently marketed products, Ortho Tri-Cyclen 21 and 28 tablets, the proposed product lacks an indication for acne vulgaris. The recommended dose is one tablet daily. _____ is supplied in a DIALPAK Tablet dispenser or in a VERIDATE Tablet dispenser (for clinic usage), and each dispenser contains 28 tablets as follows:

- 7 white tablets contain 0.180 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 light blue tablets contain 0.215 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 dark blue tablets contain 0.250 mg of norgestimate and 0.025 mg of ethinyl estradiol.
- 7 green tablets contain inert ingredients.

II. RISK ASSESSMENT

A. EXPERT PANEL DISCUSSION

A group discussion was conducted by OPDRA to gather professional opinions on the safety of the proprietary name, _____ Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The OPDRA Expert Panel concluded that the modifier, —, could be misinterpreted as the number of days to take the drug. The Expert Panel also concluded that the modifier, — places emphasis only on one ingredient of Ortho Tri-Cyclen, ethinyl estradiol.

In addition, DDMAC did not have any concerns about the name with regard to promotional claims.

B. AERS/DQRS DATABASE SEARCHES

Since Ortho Tri-Cyclen is a product name already in use in the U.S. marketplace, the usual prescription analysis studies were not conducted. OPDRA searched the *FDA Adverse Event Reporting System (AERS)* database in order to determine any post-marketing safety reports of medication errors associated with Ortho Tri-Cyclen. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "Ortho Tri-Cyclen%," "norgestimate%," and "ethinyl estradiol%" were used to perform the searches. The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Ortho Tri-Cyclen%," "norgestimate%," and "ethinyl estradiol%." The following are the results of these searches:

1. Medication Error Reports of Name Confusion Involving Ortho Tri-Cyclen and Ortho Cyclen

- a. _____ : Date of Event 11-21-96

In a retail pharmacy setting, a pharmacist dispensed an *Ortho Cyclen* 28 tablet pack instead of the prescribed drug, Ortho Tri-Cyclen 28 tablet pack. The patient took the whole package and experienced mood swings and breast tenderness. The patient discovered the error when she returned for a refill. The dispensing pharmacist noted that the event occurred during a busy shift and also noted that these two products were located side by side on the pharmacy shelf. Ortho Cyclen is also an oral contraceptive produced by Ortho McNeil. It contains a combination of norgestimate, 0.25 mg and ethinyl estradiol, 0.035 mg.

- b. _____

According to the reporter, a prescription for Ortho Tri-Cyclen was filled with *Ortho Cyclen*. No apparent adverse effects were reported.

2. Medication Error Reports of Name Confusion Involving Ortho Tri-Cyclen and Ortho Novum

a. _____

This report involved confusion between *Ortho-Novum 7/7/7* and Ortho Tri-Cyclen. The reporter was concerned that these products can be easily confused. The reporter also recommended that Ortho Tri-Cyclen should be called "Tri-Cyclen" to prevent recurrences. The report did not describe any actual incidences of medication errors. Ortho-Novum is a triphasic oral contraceptive containing a combination of norethindrone and ethinyl estradiol.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Despite overlapping indications, active ingredients, and dosage forms, only three medication errors involving name confusion with Ortho Tri-Cyclen 21 and 28 were reported to the Agency. It is difficult to ascertain the magnitude of name confusion relating to Ortho Tri-Cyclen with only three medication error reports. Furthermore, these medication error reports did not result in serious adverse events. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Ortho Tri-Cyclen.
2. In regard to the proposed name, _____ we recognize that the modifier, _____, is used to distinguish the proposed product from the currently marketed products, Ortho Tri-Cyclen 21 and 28. However, this modifier is misleading and not useful in differentiating the proposed product from Ortho Tri-Cyclen 21 and 28 for the following reasons:

In the current market place, the modifiers used in conjunction with the oral contraceptive trade names are often used to denote the number tablets and/or days. For example, for the product, Ortho Tri-Cyclen 28, the modifier, "28", is interpreted as "28" tablets to be taken over 28 days. Therefore, the modifier, _____ could be misinterpreted as _____ ablets to be taken over _____ days. However, _____ contains 28 tablets, not _____ tablets.

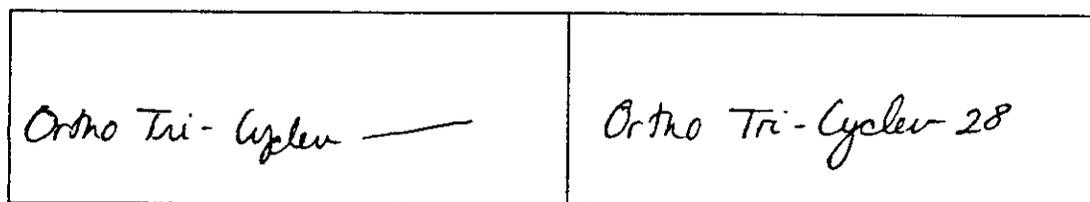
The modifier, _____, could also be misinterpreted as '_____' of the same active ingredients and strengths as the currently marketed products. _____ contains the same active ingredients as the currently marketed products, Ortho Tri-Cyclen 21 and 28. However, _____ contains a different amount of ethinyl estradiol than the currently marketed products. _____ contains 25 micrograms of ethinyl estradiol and Ortho Tri-Cyclen 21 and 28 contain 35 micrograms of ethinyl estradiol. Hence, the modifier, _____ is used to place an emphasis on 25 micrograms of ethinyl estradiol contained in the proposed product, _____ and to distinguish it from Ortho Tri-Cyclen 21 and 28. Although the modifier, _____ may have been intended to denote 25 micrograms of ethinyl estradiol, this implication is not obvious due to the misinterpretation of the modifier, _____tablets."

In addition, the proposed name, _____ expresses only the strength of ethinyl estradiol in the trade name, and does not include the strength of the progestational compound, norgestimate. Inclusion of microgram content of only the ethinyl estradiol in the proprietary name is misleading and may be confusing, because it gives the appearance that the product contains only one active ingredient. Currently, when the modifiers are used to represent the active ingredients of oral contraceptives, both progestational and estrogenic compound strengths are expressed in the trade names. For example, another Ortho McNeil product, Ortho Novum 1/35, has both ingredients expressed in the modifier, "1/35". The modifier, "1", denotes 1 milligram of

norethindrone and the modifier, "35", denotes 35 micrograms of ethinyl estradiol contained in the product, Ortho Novum 1/35.

Another important concern we have regarding the modifier, —, is that it is not enough to distinguish the proposed name from "Ortho Tri-Cyclen 21 and 28" and prevent potential medication errors. First, many practitioners just prescribe "Ortho Tri-Cyclen" without the modifiers, since the substitution of 21-day supply for 28-day supply or vice versa does not result in treatment failures. Often the patients decide to take either Ortho Tri-Cyclen, 21 or 28. If the providers forget to write the modifier, —, when ordering this proposed product, then the patients could receive Ortho Tri-Cyclen 21 or 28 instead. These products can not be substituted for one another. If a patient who is susceptible to estrogen receives the higher amount of ethinyl estradiol, it could result in adverse events such as breakthrough bleeding.

Second, — could be misinterpreted as Ortho Tri-Cyclen 28 or vice versa when written. The modifier, "28", looks very similar to the modifier, —, or vice versa when scripted as demonstrated in the following written sample of prescription:



Finally the location of these products may also contribute to the increased risk of medication errors. In pharmacy settings, all three products could be stored in close proximity to one another, since they share the same trade name, Ortho Tri-Cyclen. Therefore, the prescription orders for these drugs could be confused and result in medication errors. If these products are dispensed for one another, the patients will receive the incorrect amount of ethinyl estradiol.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the package insert, the paperboard packer tray, the pouch for dispenser, and the blister pack of — OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. PAPERBOARD PACKER TRAY LABELS

The draft paperboard packer does not indicate the color. We recommend differentiating it by using a different color paperboard from the available Ortho Tri-Cyclen 21, 28, and other Ortho McNeil oral contraceptives, since they will be located in close proximity to each other in most pharmacies. We recommend this to decrease the risk of medication errors.

B. PACKAGE INSERT LABEL

1. Indications and Usage

The statement reads, " _____ Tablets are indicated for the prevention..." This statement is misleading, because the proposed product contains 28 tablets, not _____ ablets. We recommend clarifying " _____ Tablets" here and throughout the package insert.

2. How Supplied

- a. All three " _____ " strengths will be available in the same colors, shapes, and imprints as the currently available "Ortho Tri-Cyclen 21 and 28" tablets. We recommend differentiating the proposed product tablets from the currently available product tablets by using different colors, shapes, and/or imprints, since the proposed product contains the different amount of ethinyl estradiol.
- b. The sponsor does not indicate the color of the DIALPAK. We recommend a color that is different from the currently available Ortho McNeil DIALPAKs.

IV. RECOMMENDATIONS

- A. OPDRA does not recommend the use of the proposed name, _____, for the following reasons:
 1. We do not recommend the modifier, _____; it includes only the mcg-strength of the ethinyl estradiol component in the trade name, and it could be misinterpreted as the number of tablets and/or days.
 2. The modifier, _____, is not enough to distinguish the proposed product from the available products, Ortho Tri-Cyclen 21 and 28, and prevent potential medication errors.
- B. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

**APPEARS THIS WAY
ON ORIGINAL**

cc: NDA 21-242

HFD-580; Division Files/Jennifer Mercier, Project Manager

HFD-580; Susan Allen, Division Director

HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-530; Heidi M. Jolson, Acting Deputy Center Director for Review Management

HFD-400; Martin Himmel, Deputy Director, OPDRA

HFD-040; Patricia Staub, Senior Regulatory Review Officer, DDMAC

HFD-440; Mary Dempsey, Project Manager, OPDRA

HFD-400; Sammie Beam, Project Manager, OPDRA

L:\OPDRA00\KIM\00-0209_____ .FIN.DOC

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

ORTHO TRI-CYLEN® Lo
norgestimate/ethinyl estradiol

3S

R.W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier
HFD-580
7-4260

Phase 4 Commitment

N/A

1S/
6/14/07

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYLEN® Lo
norgestimate/ethinyl estradiol

3S

R.W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier
HFD-580
7-4260

Press Release

N/A

ISI

6/14/01

**APPEARS THIS WAY
ON ORIGINAL**

ITEM 13: PATENT INFORMATION

NDA 21-241 _____ (norgestimate/ethinyl estradiol)
Tablets

Information Required in Accordance with 21 CFR§314.53

_____ (norgestimate/ethinyl estradiol) Tablets is
protected by the following:

US Patent No.	Patent Type	Expiration Date	Owner
4,530,839	Method of Use	September 26, 2003	Ortho-McNeil Pharmaceutical, Inc.
4,544,554	Method of Use	September 26, 2003	Ortho-McNeil Pharmaceutical, Inc.
4,616,006	Method of Use	September 26, 2003	Ortho-McNeil Pharmaceutical, Inc.
4,628,051	Method of Use	September 26, 2003	Ortho-McNeil Pharmaceutical, Inc.

**APPEARS THIS WAY
ON ORIGINAL**

Johnson & Johnson

OFFICE OF
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, N.J. 08933-7003

Phone (732)524-2641
Fax (732)524-5866

April 4, 2000

Re: _____ NDA No. 21-241
Information Required in accordance with 21 CFR § 314.53

Pursuant to the provisions of 21 CFR § 314.53, attached hereto please find patent information for the above identified application.

Attached item 13 lists 4 patents. The undersigned declares that U.S. Patent Nos. 4,530,839, 4,544,554, 4,616,006 and 4,628,051, owned by Applicant's parent company, Ortho-McNeil Pharmaceutical, Inc., cover the method of use of the drug product which is the subject of this application for which approval is being sought.

A claim of patent infringement could be asserted if a person not licensed by the owner of the patents listed above engaged in the manufacture, use or sale of the drug product of this application for which approval is sought.

Respectfully submitted,



Kenneth J. Dow
Registered Patent Attorney
Reg. No. 32,890

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-241 SUPPL #
Trade Name ORTHO TRI-CYCLEN Lo
Generic Name norgestimate/ethinyl estradiol
Applicant Name Johnson & Johnson Pharmaceutical Research
HFD- 580
Approval Date August 22, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-653 norgestimate/ethinyl estradiol

NDA # 19-697 norgestimate/ethinyl estradiol

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

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ON ORIGINAL**

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # NRGLOW-OC-001

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 Study # NRGLOW-OC-001
Investigation # __, Study #
Investigation # __, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 11,391 YES /X/ ! NO /___/ Explain:
!
!
!

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

**APPEARS THIS WAY
ON ORIGINAL**

cc:
Archival NDA
HFD-580/Division File
HFD-580/Mercier
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

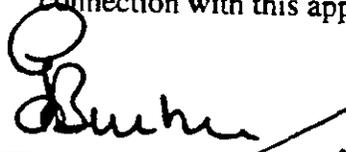
Daniel A. Shames
8/22/02 01:13:06 PM

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EDMS-USRA-4705910

ITEM 16: DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute hereby certifies that it did not and will not use in any capacity the services of any person debarred under sections 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

 21st July 2000.

Graham Burton, MD
Vice President, Regulatory Affairs
The R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Financial Disclosure
N/A

U
ISI
8/10/02

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 14, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-241

I have reviewed the financial disclosure information submitted by The R.W. Johnson Pharmaceutical Research Institute in support of their NDA 21-241 for ORTHO TRI-CYCLEN® Lo Tablets (norgestimate and ethinyl estradiol).

One pivotal Phase 3 study was conducted to assess the safety and efficacy of ORTHO TRI-CYCLEN® Lo Tablets (norgestimate and ethinyl estradiol). This product is a combined oral contraceptive and is proposed for the prevention of pregnancy. The study number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study NRGLOW-OC-001 / "A Randomized, Comparative, Multicenter, Safety and Contraceptive Efficacy Study of Two Cyclophasic™ Norgestimate/Ethinyl Estradiol Regimens, and One Triphasic Norgestimate/Ethinyl Estradiol (RWJ-01403-000) Regimen (RWJ-10131-000) and Loestrin® Fe 1/20 (Protocol NRGLOW-OC-001; Phase 3) (Doc ID EDMS-USRA- 5184909)	Completed before 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

The sponsor did not submit any Financial Disclosure data (in accordance with 21 CFR 54) in their NDA submitted August 25, 2000. A request for this data by the Division on October 18, 2000 resulted in the sponsor submitting a statement that there was no disclosable information in their studies to support this NDA. A follow-up request for appropriate financial certification and/or disclosure documentation was made by the Division on May 3, 2001 for the following:

- A table including the following information:
 - Study Number
 - Study Site

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- Number of patients enrolled at each site
- Names of investigators (principal and subinvestigators) at each site
- Financial Disclosure information received for each investigator
- Disclosable information for each investigator
- Documentation of due diligent efforts taken to obtain disclosure information from each site.

Study NRGLOW-OC-001

There were 691 principal and subinvestigators (investigators) at 111 sites (6373 subjects) in this trial; there was no one site that enrolled a majority of the subjects. The sponsor conducted a retrospective collection of the financial disclosure information for this study that was completed prior to February 2, 1999. The sponsor has submitted appropriate certification "as the sponsor of the submitted study" for the requirements under 21 CFR 54.2. The sponsor also provided evidence of due diligence (requests via federal Express, follow-up phone calls, and directory assistance) in their attempts to obtain the financial disclosure information on a retrospective basis.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

Jeanine Best
6/14/01 10:30:05 AM
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- b. The dissolution specification for ethinyl estradiol at stability should be revised to ~~_____~~ at 20 minutes.
5. The proposed expiration date of ~~_____~~ is not acceptable. Based on the real time data, 18-months can be granted when stored at 25°C (77°F).
6. Please revise the stability commitments as follows:
- Three production batches of each strength of drug product will be tested according to the stability program and at least one annual batch will be added to the stability program. The stability data will be reported in the NDA Annual Report.
 - The extension of the expiry will be based on the real time data generated from the first three production batches, otherwise, a prior approval supplement will be submitted to extend the expiry date.
7. Please make the following corrections in the physician and patient insert:
- The molecular weight of ethinyl estradiol should be revised to _____
 - Please use one of the following norgestimate chemical names as published in the USP Dictionary of USAN and International Drug Names:
 - 18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-, or
 - (+)-13-Ethyl-17-hydroxy-18, 19-dinor-17 α -pregn-4-en-20-yn-3-one oxime acetate (ester).
8. Please include the storage statement on the paperboard packer tray-front panel, on the Pouch-Back, and on the blister-back.
9. Please include the lot number and expiry date on the Pouch-Back.
10. The proposed color of the foil over wrap and packer for the finished drug product is light orange color. This color does not have enough contrast to the white color that is used for some of the printed information. Please address this concern.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Amit K. Mitra

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IR letter. Amit K. Mitra for M. J. Rhee as Acting Team Leader

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/s/

Daniel A. Shames
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/s/

Susan Allen

4/4/01 04:12:50 PM

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ON ORIGINAL



NDA 21-241

DISCIPLINE REVIEW LETTER

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

Dear Dr. Polo:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: _____ (norgestimate/ethinyl estradiol) Tablets.

Our review of the tradename of your submission is complete. The tradename was found to be unacceptable by the Office of Post-Marketing Drug Risk Assessment and the Division concurs. We have identified the following deficiencies:

1. The use of the modifier _____ refers to the mcg-strength of the ethinyl estradiol component in this drug product, and thus could be misinterpreted as the number of tablets and/or days of use.
2. The modifier _____ is not adequate to distinguish the proposed product from the other available products, Ortho Tri-Cyclen 21 and Ortho Tri-Cyclen 28, and could lead to potential medication errors.

Please propose an alternative tradename for your product. We will forward this new tradename for review by the Office of Post-Marketing Drug Risk Assessment.

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, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III

/s/

Terri F. Rumble
1/25/01 10:53:38 AM

APPEARS THIS WAY
ON ORIGINAL

Mercier

I 11,391

NDA 21-241

SEP 13 2000

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

Dear Dr. Polo:

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 Product: _____ (ethinyl estradiol/norgestimate) tablets
Review Priority Classification: Standard (S)
Date of Application: August 25, 2000
Date of Receipt: August 25, 2000
Our Reference Number: NDA 21-241

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 October 24, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 25, 2001 and the secondary user fee goal date will be August 25, 2001.

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

NDA 21-241
Page 2

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

Sincerely,

(/S/

9/11/0

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

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

Page 3

cc:

Archival NDA 21-241

HFD-580/Div. Files

HFD-580/JM

HFD-580/Allen/Mann/Shames/Willett/Monroe/Jordan/Kammerman/Rhee/Boal/Parekh/Jarugula
DISTRICT OFFICE

Drafted by: JM/September 8, 2000

Initialed by: Rumble9.8.00

final: September 11, 2000

filename: 21241.WPD

ACKNOWLEDGEMENT (AC)

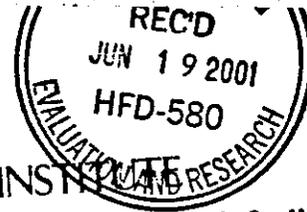
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ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



18 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 21-241
ORTHO TRI-CYCLEN® Lo
Tablets (norgestimate and
ethinyl estradiol)

BL

NDA ORIG AMENDMENT

Amendment to a Pending
Application:
Labels/Labeling Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for ORTHO TRI-CYCLEN® Lo Tablets, a combination progesterone/estrogen tablet for the . Reference is also made to the FDA comments that we received on 14 June 2001, on our draft labeling contained in the NDA. At this time we would like to provide comments on the proposed changes as well as our suggested revisions for your consideration. The document has been temporarily re-formatted to allow for a column containing PRI's justification for the revisions. As you will note at the top of the pages, red strikeout and blue double-underline were changes and/or comments recommended by FDA. Yellow highlighted text represents changes proposed by PRI.

We would also like to clarify that we plan to have a separate label for ORTHO TRI-CYCLEN® Lo. The labeling for this product will not be combined on the insert with CYCLEN and TRI-CYCLEN®. We have considered your proposal to but are unable to do so at this time due to time constraints. We will however, entertain this suggestion in the future.

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:	
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CSO INITIALS	DATE

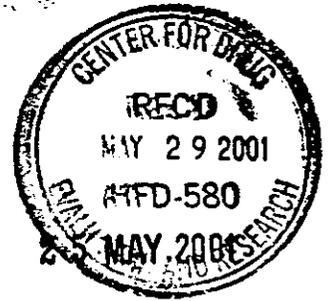
Desk copy was faxed to Jennifer Mercier, DRUDP, HFD 580 on 18 June 2001.



ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



BB

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 21-241

Tablets (norgestimate and
ethinyl estradiol)

**Amendment to a Pending
Application:**
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the [redacted]. Reference is also made to Dr. Venkat Jarugula's 24 May 2001 request to provide additional information. At this time we wish to provide the following information 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 4.0.4139.

- Demographic data for the following Phase 1 NRGLOW studies:
 - PHI-001
 - PHI-002
 - PHI-003
 - PHI-004
- SAS transport file, [redacted] has been corrected to reflect the pharmacokinetic data, not the concentration data.

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.

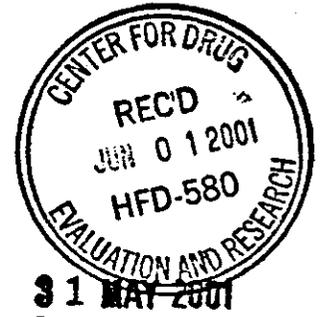
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ZURICDATE

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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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:
Response to Request for
Information

ORIG AMENDMENT

BL

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____

Reference is also made to Ms. Mercier's 30 May 2001 request to provide a copy of the annotated label (Item 3, Chapter 1). A copy of this Chapter is provided with this submission and may be found in the original application as Item 3, Volume 1 of 1, Chapter 1, Pages 1-60 (Overall Volume 3 of 71). Please note that as agreed to on 01 August, 2000, only new or modified labeling information was annotated. This new information was presented as italicized and underlined text. The remainder of the labeling information was identical to the currently marketed ORTHO CYCLEN[®]/TRI-CYCLEN[®] labeling.

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:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Desk copy to Jennifer Mercier, DRUDP, HFD 580

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



29 MAY 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 21-241

Tablets (norgestimate and
ethinyl estradiol)

BM

NDA ORIG AMENDMENT

Amendment to a Pending
Application:
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____
Reference is also made to Ms. Mercier's 24 May 2001 request to provide additional information for the Medical Reviewer. At this time we wish to provide a table containing the following information which was requested:

- A breakdown of subjects 35 years and under who completed 13 cycles of treatment, and a breakdown of subjects 35 years and under who completed 6 cycles of treatment.

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

Desk copy to Jennifer Mercier, DRUDP, HFD 580

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08859-0602



ORIGINAL

10 APR 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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:

Response to Request for
Information

ORIG AMENDMENT

Dear Dr. Allen:

BM

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____
_____. Reference is also made to requests on 21 March and 29 March for additional clinical/statistical data. At this time we wish to provide these data for the Medical Reviewer. A list is provided on page 01 00001; it identifies the data provided in this submission, as per the 21 March request. A list is also provided on page 01 00007; it identifies the data provided in this submission, as per the 29 March request.

Should you have questions regarding this submission, please contact me directly 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	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

05 APR 2001

Susan Allen, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-241

(norgestimate and ethinyl estradiol
tablets)

AMENDMENT TO A
PENDING APPLICATION
Chemistry, Manufacturing and
Controls Information

Dear Dr. Allen:

Reference is made to our pending NDA 21-241 for _____ submitted on August 25, 2000. Reference is also made to a telephone conversation between J. Mercier and V. Donnelly on 5 April 2001 regarding a RW Johnson Pharmaceutical Research request to submit 18-month drug product stability data. Upon discussion with the reviewing chemist, Ms. Mercier confirmed acceptance of the data without impeding or extending the 10-month review period.

The stability protocol had been amended to add an additional condition of 30C/60%RH at 18-month to conform to ICH. Attached for your review is the 18-month drug product stability data. All data is within specifications and is deemed acceptable.

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 Valerie Donnelly at (908) 704-5891 or myself at (908) 704-4812 or our dedicated FDA number (908)-704-4600 if you have questions regarding this information.

Sincerely,

Ramon Polo, Ph.D.
Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

Desk Copy: J. Mercier

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



01 MAR 2001

NEW CORRESP

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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the . Reference is also made to the Agency's 12 January 2001 request to provide additional information for the chemistry reviewer. This information was provided as an amendment to a pending application on 22 January 2001. At this time however, we wish to revise the amendment with the following information.

CMC Table 4.36 Facilities Involved in Testing, Labeling and Warehousing of Drug Product:

This table has been revised to remove the following test site.

Ortho-McNeil Pharmaceutical, Inc.
Welsh and McKean Roads
Spring House, Pennsylvania 19477-0776

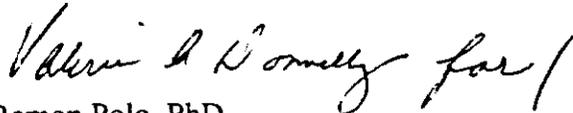
This site will not perform drug product release or stability testing. Such testing will be done at the Ortho-McNeil Pharmaceutical, Inc., Raritan, New Jersey site. We apologize for any confusion that this may have caused. A copy of the revised table is provided in this submission.

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.

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

Copy sent on 01 March 2001 via fax to Jennifer Mercier, Project Manager, DRUDP

**APPEARS THIS WAY
ON ORIGINAL**

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

We would ask that this name be given an expedited review by OPDRA, as our primary user fee goal is June 25, 2001. Should you have any questions, please contact me directly at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our phone number dedicated to FDA use (908) 704-4600.

Sincerely,

Jeri Williams for

Ramon Polo, PhD

Director

Regulatory Affairs

One desk copy to: Jennifer Mercier, Project Manager, DRUDP

**APPEARS THIS WAY
ON ORIGINAL**



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



ORIGINAL

NEW CORRESP

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 21-241

Other:

Response to FDA Request For
Information, Additional Desk
Copy

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241 for _____
_____ tablets, a combination progestin/lower dose estrogen
contraceptive indicated for the prevention of pregnancy in women who elect to use
oral contraceptives as a form of contraception. At this time we wish to provide, as
per your request, an additional desk copy of the unannotated labeling (Item 2). This
information, which was also provided in the original application on CD-ROM, is
provided here on a diskette in Microsoft WORD format. This diskette 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

REVISIONS COMPLETED

CSO ACTION: N.A.I. MEMO

LETTER

CSO INITIAL: JS DATE: 1/10/01

Desk Copy: Send to Jennifer Mercier at FDA, DRUDP

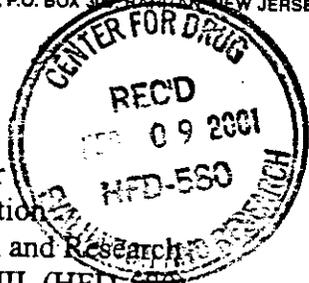


ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

0 8 FEB 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 21-241

Tablets (norgestimate and ethinyl estradiol) **ORIG AMENDMENT**

BB

Amendment to a Pending Application:

Response to Request for Information

Noted
NAI
URO
2/11/01

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the . Reference is also made to a request for a clinical study update on "The Effect of Tetracyclines on the Pharmacokinetics of Ethinyl Estradiol in Women Using Ortho-TriCyclen" Study Protocol CAPSS-042 by Jennifer Mercier, CSO, FDA, on 01 February 2001. At this time we wish to inform you that this clinical study was not intended to support this NDA 21-241. However, to address the FDA request, this study had been discontinued prior to patient enrollment. Therefore, no study report has been written.

Should you have any further questions regarding Study CAPSS-042 please contact William Sisco at (908) 704-4301. Please contact me directly for NDA related questions at (908) 704-4812, or 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

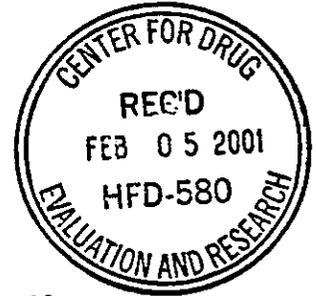
REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS <i>JP</i> <i>2/8/01</i> DATE

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



26 JAN 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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:

Request for a Type A Meeting

Dear Dr. Allen:

MR

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____ . Reference is also made to the Information for Consultation with the Office of Post Marketing Drug Risk Assessment (OPDRA) submission, dated 10 April 2000 and their subsequent decision to not accept the proposed trademark, _____ which was communicated to us verbally during a telephone conversation between Jennifer Mercier and Valerie Donnelly on 17 January 2001. We appreciate this telephone notification in advance of the written communication.

Though we are still awaiting formal, written notification of the rejection of our proposed trademark, the reasons cited verbally for OPDRA's objection to the _____ trademark were twofold: 1) that the use of — would be confusing, because it might be mistaken with our other products and could connote a _____ regimen; 2) that the use of — in the product name only reflects one of the two active drug substances and thus does not accurately represent the drug product.

We acknowledge the concerns raised by the Division and OPDRA, and we would like to present to the Division information which explains why we had selected this trademark, as well as important actions which we have taken subsequent to our submission of the trademark to FDA, in order to address the concern over confusion. That information is summarized briefly below.

Confusion with number of dosing days: discontinuation of ORTHO TRI-CYCLEN®
21

As a therapeutic class, 98.5% of all oral contraceptive prescriptions are dispensed as 28-day regimens; 21-day regimens represent even less than 1.5% of all cycles

dispensed in the Ortho-McNeil product line. Nonetheless, we also anticipated the potential for confusion over the use of _____ in the trademark, since both 21- and 28-day regimens exist. Thus, as a company, we elected to discontinue all 21-day put-ups throughout our entire oral contraceptive line. We have informed health care providers, pharmacists, and the trade of this decision. We have also instructed health care providers that they do not need to indicate "28" on their prescriptions for OCs, as well. This communication occurred via letter and through our field sales force. A copy is provided here for ease of review behind the tab titled, "Attachment A". As noted in our 17 January 2001 submission, Ortho McNeil Pharmaceutical has discontinued the 21-day regimen for our entire line of oral contraceptives. A copy of this submission is also provided here for ease of review behind the tab titled, "Attachment B".

Currently, the ORTHO TRI-CYCLEN[®] line consists of only 28-day packs. If approved, _____ would also consist of 28-day packs only. The potential for either dispensing errors or dosing errors arising from ambiguity around the number of days in a cycle of OCs should be negligible now that all of our OC products will reflect the same, 28-day dosing regimen. (See enclosed sample behind the tab titled, "Attachment C", of ORTHO TRI-CYCLEN[®] and preliminary mock-up of _____ Dialpaks, which illustrate clear denotation of the 28-day regimen in plain sight of the trademark itself.) We believe that this action effectively addresses OPDRA's concern over potential confusion among our consumers, physicians and pharmacists.

Appropriate Description of Drug Product by Trademark:

We believe that _____ is the name that most accurately describes the product. The type, dose, and triphasic regimen of the progestin component is identical to our currently marketed ORTHO TRI-CYCLEN[®]. In fact, the foundation of the name of our new product accurately describes the regimen: "TRI" describes the triphasic regimen and "CYCLEN" describes the progestin component. Taken together, the name connotes the widely-held knowledge that the progestin dose given is 180-215-250 mcg, each given for 7 days. All CYCLEN OCs contain norgestimate, just as all "Ortho Novum" OCs contain norethindrone. Physicians have clearly indicated to us their expectation that new drugs within an OC product line containing the same progestin would bear the same root name as the original OC.

Additionally, there are other products that have numerical suffices that only describe the estrogen component: OVCON[®] 35 and OVCON[®] 50 as an example. We have substantive plans to educate pharmacists and health care providers about this product. The logo would clearly indicate "28 day regimen". We believe that these observations speak directly to the second concern raised by OPDRA, namely, that the numerical suffix refers only to the estrogen component of the product.

Rather than enter immediately into a formal appeal process, we had preferred simply to engage in a dialogue with the Division, to determine whether these data and actions would mitigate their concerns, and to consider additional steps which could be taken to satisfy any remaining objections. This in order to expedite the process of securing a final trademark for this product, which is now moving forward through a 10-month

review process, with an action date in June. Should the product receive a favorable review, we anticipate beginning _____

As we are dealing with a new trademark approval process at FDA, we wish to move forward in the most expeditious fashion consistent with that procedure. As such, we have requested a teleconference with you through Jennifer Mercier to explore these issues and seek the guidance of the Division. Ms. Mercier has rejected our verbal request for such a teleconference, and _____ but did insist that if we remain committed to pursuing a discussion with the Division, rather than proceeding with an appeal, that we submit a written request for such a meeting. We would be perplexed and dismayed should the Division refuse to entertain a collaborative discussion on this subject, and accordingly we have followed her instructions and are submitting herein this written request for a Type A meeting --- either face-to-face or via teleconference --- at the Division's earliest convenience.

Purpose of Meeting

To discuss information not known to FDA during trademark review.

Objectives/Expected Outcomes for Meeting

- 1) To determine whether rejected brand name might now be acceptable in light of new information.
- 2) If not acceptable, to gain insight into what types of alterations to existing brand name proposal are likely to be acceptable to Division and to OPDRA.

Proposed Agenda:

- 1) impact of new information, i.e., ORTHO TRI-CYCLEN® 21-day product withdrawal and feedback obtained from consumers and physicians, on the Division's view of the proposed trademark --- 15 minutes
- 2) any additional concerns which OPDRA or the Division may still have over the existing proposal, and appropriate actions which could address these concerns --- 15 minutes
- 3) if necessary, the need to file alternative trademarks for review, and the optimum timing for such submissions vs. pursuit of an appeals process --- 15 minutes

Planned External Attendees

Gary Shangold, MD	Vice-President, Regulatory Franchise Leader, RWJPRI
Ramon Polo, PhD	Regulatory Project Leader, RWJPRI
Valerie Donnelly	US Regulatory Manager, RWJPRI
Trent Gardner	Director of New Product Development, Ortho-McNeil Pharmaceutical
Ray Suehnholz	Vice-President, Marketing Analytics, Ortho-McNeil Pharmaceutical

Requested FDA Participants

Susan Allen, MD	Director, Division of Reproductive and Urologic Drug Products, FDA
Jennifer Mercier	Project Manager, Division of Reproductive and Urologic Drug Products, FDA
Jerry Phillips	OPDRA, FDA

Submission of Supporting Documentation

Should the Division feel it would be helpful to them in the proposed discussion, we are prepared to forward summaries of qualitative consumer and physician research conducted by Ortho-McNeil in the process of trademark selection immediately.

Should you have any questions and/or comments, please contact me directly at (908) 704-5148, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600. We look forward to a response at your earliest convenience. Thank you.

Sincerely,



Gary A. Shangold, MD
Vice-President, Regulatory Franchise Leader
The R. W. Johnson Pharmaceutical Research Institute

Desk copy of letter only was faxed to Ms. Jennifer Mercier on 26 January 2001

**APPEARS THIS WAY
ON ORIGINAL**

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	<input checked="" type="checkbox"/>
CSO INITIALS	DATE
/S/	[Signature]

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

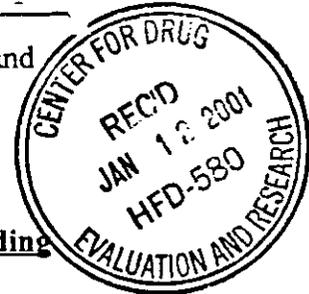
JAN 11 2001

BS
ORIG AMENDMENT

NDA 21-241

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

Tablets (norgestimate and
ethinyl estradiol)



Amendment to a Pending
Application:
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the prevention of pregnancy. Reference is also made to the Agency's 28 December 2000 request to provide additional information for the medical reviewer and the statistical reviewer. At this time we wish to provide the following information.

Clinical Information:

In the Clinical Study Report for Protocol NRGLOW-OC-001 (Item 8, Item Volume 16, page 270), reference is made to the exclusion of Site 011 from the data analyses due to reports that this site was not adhering to Good Clinical Practice regulations. Additional details as per the Medical Reviewer's request are as follows.

The investigational Site 011 was that of _____ . The site address was _____ His site was terminated from the NRGLOW-OC-001 study on 09 January 1998 while the study was ongoing. A teleconference was held on 02 April 1998 between representatives of the R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and representatives of the FDA including Dr. Gus Turner, Division of Scientific Investigations (DSI), Dr. Bette Barton (DSI), and Lana Pauls (Division of Reproductive and Urologic Drug Products). The purpose of the teleconference was to inform the FDA of the data integrity issues discovered during monitoring and audit visits, which led to the decision to terminate the site. During the teleconference, Dr. Turner requested documents which were provided to FDA in a submission dated 06 May 6 1998. A copy of the cover letter of this submission is provided for ease of review behind the tab titled, "Correspondence 06 May 1998". The cover letter lists specifically, the information that was included in the 06 May 1998 submission.

Statistical Information:

As requested by the Statistical Reviewer in a fax dated 28 December 2000, we are providing electronic files for Study NRGLOW-OC-001. Please note however, that this information was submitted in the original application and thus we are not providing an Archival copy in this submission. Rather, we are providing a copy of the CD-ROM in a green Statistical jacket only. In addition, to aid the review, we are also providing a table that lists where the data can be located. This table, located behind the tab titled, "CD-ROM Descriptions", lists the variables requested by FDA under the "Description" column. It also lists the variable name and dataset where the data may be found. If applicable, a "Qualifier" is provided in the first column of the table.

We hope that you will find this information acceptable. 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

Note: CD-ROM provided in green statistical jacket; archival copy not provided in this submission.

**APPEARS THIS WAY
ON ORIGINAL**

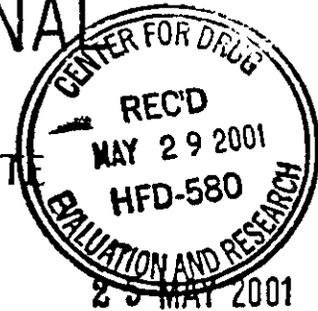
REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



NDA ORIG AMENDMENT ⁷ ml

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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:

Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____
_____ Reference is also made to Ms. Mercier's 24 May 2001 request to provide additional information for the Medical Reviewer. At this time we wish to provide the following information on Site 11.

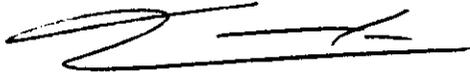
Clinical Information:

In the Clinical Study Report for Protocol NRGLOW-OC-001 (Item 8, Item Volume 16, page 270), reference is made to the exclusion of Site 011 from the data analyses due to reports that this site was not adhering to Good Clinical Practice regulations. Additional details as per the Medical Reviewer's request are as follows.

The investigational Site 011 was that of _____ . The site address was _____
_____ His site was terminated from the NRGLOW-OC-001 study on 09 January 1998 while the study was ongoing. A teleconference was held on 02 April 1998 between representatives of the R.W. Johnson Pharmaceutical Research Institute (RWJPRI) and representatives of the FDA including Dr. Gus Turner, Division of Scientific Investigations (DSI), Dr. Bette Barton (DSI), and Lana Pauls (Division of Reproductive and Urologic Drug Products). The purpose of the teleconference was to inform the FDA of the data integrity issues discovered during monitoring and audit visits, which led to the decision to terminate the site. During the teleconference, Dr. Turner requested documents which were provided to FDA in a submission dated 06 May 6 1998. A copy of the cover letter of this submission and a list of its contents was also provided to FDA on 11 January 2001.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

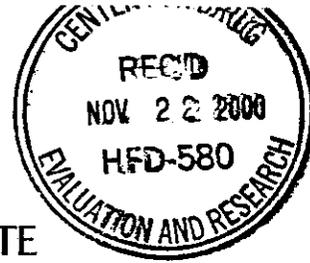


Ramon Polo, PhD
Director
Regulatory Affairs

Desk copy of CD-ROM to Dr. Venkateswar Jarugula, PK Reviewer, HFD 580

APPEARS THIS WAY
ON ORIGINAL

BM
ORIG AMENDMENT



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NOV 21 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
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-241

(norgestimate/ethinyl estradiol)

**AMENDMENT TO A PENDING
APPLICATION**
Request for Information

Dear Dr. Allen:

Reference is made to our pending NDA 21-241 (norgestimate/ ethinyl estradiol). Reference is also made to a request for additional financial disclosure information from Lana Pauls, FDA to Valerie Donnelly, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI), on 18 October 2000. As per 21 CFR 54, RWJPRI certifies that the following requirements have been met:

- Compensation: RWJPRI did not provide more money for a favorable trial outcome nor did we as the sponsor, provide compensation tied to the sales of the product.
- Proprietary interest: RWJPRI did not use an investigator who had a proprietary interest in our product, license, patent, etc. This would bias him and the data from his site.
- Significant payments: RWJPRI did not provide payments >25,000 US dollars to an investigator or institution to support the activities of the investigator during or after the study period.

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

Sincerely,

Valerie Donnelly
Manager
Regulatory Affairs

cc fax desk copy: Lana Pauls

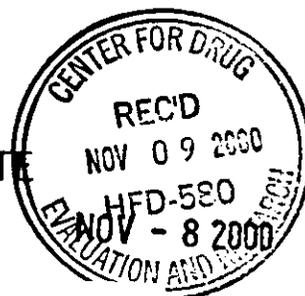
REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



Susan Allen, M.D., 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-241

(norgestimate and ethinyl estradiol
tablets)

AMENDMENT TO A
PENDING APPLICATION
Chemistry, Manufacturing and
Controls Information

ORIG AMENDMENT

Dear Dr. Rarick:

BC

Reference is made to our pending NDA 21-241 for _____ and
to our Chemistry, Manufacturing and Controls (CMC) Pre-NDA Meeting on 04
October 1999 under IND 11,391. During the meeting, we proposed _____

Drs. Lisa
Rarick, David Lin and Moo-Jhong Rhee, FDA, accepted our proposal and agreed that
submission of additional stability data would not add more time to the review of the
NDA as long as the data was submitted within six months of the original application.
The 12-month stability data for the drug product is provided with this submission. In
addition, minor errors were corrected regarding the contract testing laboratories.

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 Valerie Donnelly at (908) 704-5891 or myself at (908) 704-4812 or our
dedicated FDA number (908)-704-4600 if you have questions regarding this
information.

Sincerely,

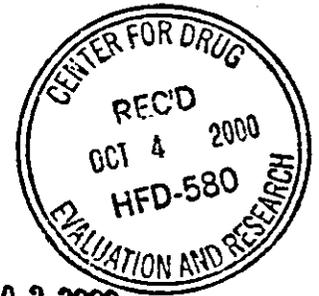
Ramon Polo, Ph.D.
Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



OCT 03 2000

Jennifer Mercier, Project Manager
Division of Reproductive and Urologic
Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II, HFD-580
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-241

ORIGINAL

Request for Information
Additional Copies of NDA

NEW CORRESP

x/c

Dear Ms. Mercier:

Reference is made to our New Drug Application 21-241 for _____
(norgestimate and ethinyl estradiol) Tablets submitted on August 25, 2000. As per your
request, enclosed are two copies each of volume 1.1, Integrated Summary of Safety and
Integrated Summary of Efficacy.

If you require additional information please contact me at (908) 704-5891 or Karen
Futterknecht at (908) 704-4912.

Sincerely,

Valerie Donnelly
Manager
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS <i>MDK</i> DATE <i>10/5/00</i>

N:\norgesti\l\tr\ndarequest\kf

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RARITAN

SPRING HOUSE

ZURICH

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

25 JUN 2002

Daniel Shames, 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 21-241
ORTHO TRI-CYCLEN[®] Lo
Tablets (norgestimate and
ethinyl estradiol)

Amendment to an
Approvable Application:
Class 1 Resubmission/Complete
Response to an Action Letter

Dear Dr. Shames:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____

Reference is also made to the Agency's Approvable Action Letter received on 25 June 2001 (provided as Attachment A in this submission for ease of review) and the sponsor's response letter dated 03 July 2001. Our response letter as required under 21 CFR 314.110, notified you of our intention to file an amendment and address the deficiencies listed in the Action Letter.

At this time, we would like to provide the amendment. It includes revised draft labeling and an NDA Safety Update Report for ORTHO TRI-CYCLEN[®] Lo. This submission provides our complete response to the deficiencies listed in the previous action letter, including numbers one through seven.

Proposed labeling revisions, found under the heading **INDICATIONS AND USAGE**, are outlined below.

I

Number of Pages Redacted 1



Draft Labeling
(not releasable)

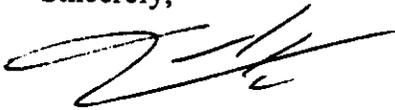
I

For ease of review and revision, the label is provided in WORD format, on hard copy and CD-ROM. The CD-ROMs were scanned and deemed virus-free using McAfee Vshield program version 4.5.1, scan engine version 4.1.60, virus definition 4.0.4199.

Also included in this submission, behind the tab titled "NDA Safety Update", is a Safety Update as per 21 CFR, 314.50(d)(5)(vi)(b).

Should you have any questions and/or comments, please contact me directly 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

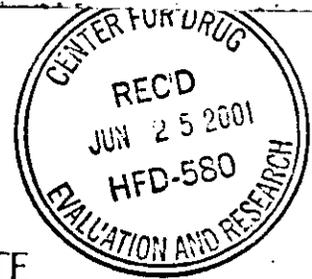
Send 1 desk copy and 1 CD-ROM copy to Jennifer Mercier, DRUDP, HFD 580

**APPEARS THIS WAY
ON ORIGINAL**



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



22 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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:

Response to Request for Clinical
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for . Reference is also made to Ms. Mercier's 20 June 2001 request to provide the Medical Reviewer, additional bleeding data. As per this request we are submitting, "the percent of subjects in each cycle that had more than seven days of bleeding and/or spotting for both ORTHO TRI-CYCLEN[®] Lo and Loestrin[®]". This data is appended to this submission in tabular format.

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

Desk copy was faxed to Jennifer Mercier, DRUDP, HFD 580 on 21 June 2001.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
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

APPLICANT INFORMATION

NAME OF APPLICANT

The R.W. Johnson Pharmaceutical Research Institute

DATE OF SUBMISSION

22 JUN 2001

TELEPHONE NO. (Include Area Code)

(908) 704-4812

FACSIMILE (FAX) Number (Include Area Code)

(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 21-241

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

norgestimate/ethinyl estradiol

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM: tablet

STRENGTHS:

180 mcg norgestimate/25 mcg ethinyl estradiol
215 mcg norgestimate/25 mcg ethinyl estradiol
250 mcg norgestimate/25 mcg ethinyl estradiol

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

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 Response to FDA Request for Clinical Information

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.

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

IND 11,391; IND 50,488; NDA 19-697; NDA 19-653; NDA 21-040

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) **Response to FDA Request for Clinical Information**

CERTIFICATION

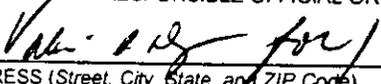
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, Warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as Requested by FDA. 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 Ramon Polo, PhD Director, Regulatory Affairs	DATE 2 2 JUN 2001
ADDRESS (Street, City, State, and ZIP Code) 920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602		Telephone Number (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.

**ORTHO TRI-CYCLEN LO
TOTAL BLEEDING INFORMATION**

Cycle	Bleeding/ Spotting	Ortho Tricyclen Lo		Loestrin	
		% of subjects with occurrence	% of subjects with a duration > 7 days	% of subjects with occurrence	% of subjects with a duration > 7 days
1	IMB	32%	6%	46%	8%
	Menstrual	96%	16%	79%	7%
2	IMB	27%	3%	40%	5%
	Menstrual	96%	11%	83%	7%
3	IMB	24%	3%	37%	5%
	Menstrual	96%	10%	84%	8%
4	IMB	25%	2%	34%	3%
	Menstrual	96%	10%	82%	4%
5	IMB	23%	3%	33%	3%
	Menstrual	95%	8%	80%	5%
6	IMB	21%	2%	33%	3%
	Menstrual	98%	7%	79%	4%
7	IMB	17%	2%	29%	2%
	Menstrual	96%	6%	81%	3%
8	IMB	20%	2%	27%	1%
	Menstrual	97%	7%	76%	3%
9	IMB	19%	1%	27%	1%
	Menstrual	98%	9%	81%	4%
10	IMB	21%	3%	28%	3%
	Menstrual	96%	10%	77%	5%
11	IMB	18%	1%	30%	2%
	Menstrual	97%	8%	81%	5%
12	IMB	20%	1%	28%	3%
	Menstrual	96%	9%	74%	4%
13	IMB	20%	2%	27%	1%
	Menstrual	NC	NC	NC	NC

IMB = intermenstrual bleeding/spotting

NC = not calculated

**APPEARS THIS WAY
ON ORIGINAL**

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 U.S. Route # 202, P.O. Box 300
Raritan, New Jersey 08869-602

TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499DATE: 21 June 2001TO: JENNIFER MERCIER
Project Manager, FDA
Div. Reprod. & Urol. Drug ProductsFROM: Valerie Donnelly
Regulatory Affairs
Phone: (908) 704-5891
Fax: (908) 203-1499

TELEFAX #: (301) 827-4267

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 5

NOTE: If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

MESSAGE (If any):

JENNIFER,

RE: NDA 21-241 ORTHO TRI-CYCLEN Lo Labeling revisions

I am faxing you this desk copy correspondence, outlining our position on the newly proposed contraindication, "heavy smoking (≥ 15 cigarettes per day) and over age 35". If you have additional questions or comments on this submission, please call me at (908) 704-5891 or call Gary Shangold directly at (908) 704-5148 or call our phone line dedicated for FDA use (908) 704-4600. THANKYOU

AN OFFICIAL COPY was also faxed to Dr. Susan Allen

CONFIDENTIALITY NOTICE

This facsimile transmission cover sheet and any documents which may accompany it contains information from Johnson & Johnson, which is intended only for the use of the individual or entity to which it is addressed and which may contain information that is privileged, confidential, and/or exempt from disclosure under applicable law. If the reader of this message is not the intended recipient, any disclosure, dissemination, distribution, copying, or other use of this communication or its substance is prohibited. If you have received this communication in error, please call us collect to arrange for the destruction of the communication or its return to us at our expense. Thank you.

APPEARS THIS WAY
ON ORIGINAL



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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:

Labels and Labeling Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the
 Reference is also made to Ms. Mercier's conversation noting that there were potentially problematic issues with the label.

We strongly urge the Division to reconsider the decision to contraindicate oral contraceptives in women over the age of 35 who smoke heavily and to take the issue of a new Contraindication regarding smoking to an Advisory Committee as a matter of significant public health import and on which there are strong diverging views in the medical community. Standard of medical practice and authoritative medical guidelines have consistently treated the subject as a *relative* contraindication, where risk/benefit may be justified in a defined set of clinical circumstances as assessed by the treating physician. See ACOG Practice Bulletin # 18, July 2000 and the ACOG Technical Bulletin # 198, October 1994.

A contraindication defines a situation in which the drug should not be used because the risk of use clearly outweighs any possible benefit. In addition, [Absolute] Contraindications ordinarily apply to conditions (i.e., diseases) or situations (i.e., concomitant drug prescribing) that are able to be ascertained by the physician through proper interview, examination, and diagnosis. The amount of smoking is completely under the control of the patient, and could change from month to month. Physicians may not always have accurate information about the number of cigarettes smoked per day by their patients. A Contraindication for an amount of smoking could require physicians to have regular monthly contact with their OC patients to continue to confirm that there is no reason to immediately discontinue OC use, or it could result

in physicians refusing to prescribe OC's to smokers to avoid liability. Refusing to prescribe OC's to smokers could result in an increase in unwanted pregnancy.

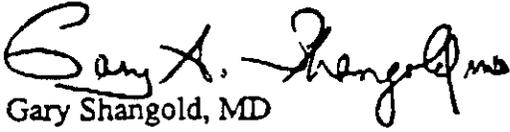
We also advise the Division, that in the face of a contraindication - with which we disagree - we will be required for medical, ethical, and legal reasons to take important immediate steps. First, we would concurrently adopt the contraindication across our product lines and would strongly petition the Agency through all available means to compel every manufacturer to do the same immediately. Second, we would issue a Dear Doctor letter and a press release advising practitioners that they should immediately contact all patients over the age of 35 to ascertain their smoking status and advise that all patients meeting the contraindication be immediately discontinued from therapy.

Clearly, this issue is of such scope and magnitude that this decision should be undertaken only with a clear consensus of the expert community and across all products in this therapeutic category simultaneously. For these reasons we again urge the Division to consider referring this to an Advisory Committee.

We look forward to receiving the Division's responses on this issue as well as the remaining issues in the label, as suggested by the Agency, by early afternoon on 22 June. Should you have any questions and/or comments, please contact me directly at (908) 704-5148 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R. W. Johnson Pharmaceutical Research Institute


Gary Shangold, MD
Vice President,
Regulatory Affairs

Desk copy was faxed to Jennifer Mercier, DRUDP, HFD 580 on 21 June 2001

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
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

APPLICANT INFORMATION

NAME OF APPLICANT The R.W. Johnson Pharmaceutical Research Institute		DATE OF SUBMISSION
TELEPHONE NO. (Include Area Code) (908) 704-5148		FACSIMILE (FAX) Number (Include Area Code) (908) 526-5059
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 21-241		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) norgestimate/ethinyl estradiol	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: tablet	STRENGTHS: 180 mcg norgestimate/25 mcg ethinyl estradiol 215 mcg norgestimate/25 mcg ethinyl estradiol 250 mcg norgestimate/25 mcg ethinyl estradiol	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE:		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 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) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> EFFICACY SUPPLEMENT			
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION LABELS/LABELING INFORMATION			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED _____	THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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.			

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 11,391; IND 50,488; NDA 19-697; NDA 19-653; NDA 21-040

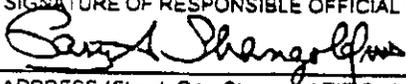
This application contains the following items: (Check all that apply)

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

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 Gary Shangold, MD Vice President, Regulatory Affairs	DATE 6-21-01
ADDRESS (Street, City, State, and ZIP Code) 920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602		Telephone Number (908) 704-4812

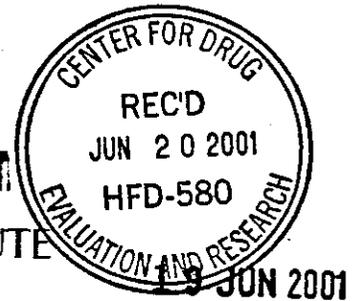
Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments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

DUPLICATE

NDA ORIG AMENDMENT
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 21-241
ORTHO TRI-CYCLEN® Lo
Tablets (norgestimate and
ethinyl estradiol)

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

10-15M

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for ORTHO TRI-CYCLEN® Lo Tablets, a combination progesterone/estrogen tablet for . Reference is also made to FDA's verbal requests on 13 June 2001 and 18 June 2001 and written request on 14 June 2001, to provide clarification of our bleeding pattern data. This clarification and the location of it in the original NDA is provided in this submission. Also included in this submission are 3 pages of data from the original NDA, which are located in the Attachments to the pivotal study report, NRGLOW-OC-001. We hope that the information provided below provides the clarification requested.

The attached tables from the NRGLOW-OC-001 clinical study report (Attachments 10a, 15a, and 17) summarize all episodes of bleeding (and non-bleeding) for the intent-to-treat population.

- **Attachment 10a** summarizes by treatment and per cycle, the percent of subjects with intermenstrual bleeding (unexpected bleeding) as well as the mean and median number of days for those subjects with intermenstrual bleeding.
- **Attachment 15a** summarizes by treatment and per cycle, the mean number of days of withdrawal flow (expected bleeding).
- **Attachment 17** summarizes the percent of subjects without withdrawal flow (unexpected non-bleeding).

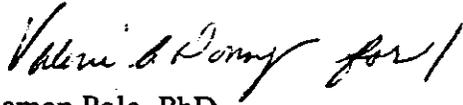
The parameters summarized in the three Attachments above were explained in the NRGLOW-OC-001 study report included in the original NDA (Item 8, volume 12, page 53, paragraph 3). Intermenstrual bleeding included breakthrough bleeding and spotting and early withdrawal flow but excluded withdrawal flow continuing from the previous cycle. Duration of menses included any bleeding or spotting during the

inactive tablet-taking interval plus withdrawal flow that continued into the next cycle. Together, intermenstrual bleeding and menses describes all bleeding associated with a given cycle.

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

Desk copy was faxed to Jennifer Mercier, DRUDP, HFD 580 on 19 June 2001.

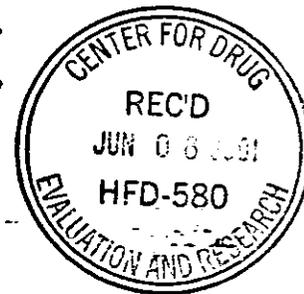
APPEARS THIS WAY
ON ORIGINAL



DUPLICATE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



08 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 21-241

Tablets (norgestimate and
ethinyl estradiol)

BL, SU

NDA ORIG AMENDMENT

Amendment to a Pending
Application:

Response to Request for
Information/and
Labels and Labeling Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the . Reference is also made to Ms. Mercier's 30 May 2001 request to provide an additional Safety Update and label annotation for the sentence under the heading, Special Populations that reads, "*In clinical studies involving 1688 subjects with a mean BMI of 23.7 (3.9) there was no association between pregnancy and either BMI or age.*" At this time, we wish to provide the following information.

NDA SAFETY UPDATE REPORT

We have no additional safety information to report. All studies were completed as of 10 July 1998 and all safety data was included in the NDA. An official submission as per 21 CFR 314.50(5)(d)(vi)(b), is provided behind the tab titled, **Attachment 1**.

LABEL ANNOTATION

In response to the label annotation question, a faxed copy of the page from the annotated label found in the original application (Item 3/Volume 1/Page 6) was faxed to the Agency on 30 May 2001 followed by a paper copy submission.

Upon further review, an error was noted in this sentence of the label. In addition, a similar sentence in the NDA Chapter Summary 6 was noted to contain the same error. Both the label and the Chapter 6 Summary have been revised to reflect a change in the denominator **from to 1673**. Additionally, we propose to revise the prognostic factor listed in the same sentence of the label **from to weight**. As a result, the following additional attachments are provided in this submission:

RRARUSRARES01PRJUSREGWORGESTINLTR060701 resp to nda req for clinical data.doc/07 June 2001/JU

LA JOLLA

RARITAN

SPRING HOUSE

ZURICH

- **Attachment 2:** A revised copy of the label. The revision appears on page 4 of the label and is identified using the highlight/strikeout feature of Microsoft WORD.
- **Attachment 3:** A revised copy of annotated page 5 from the Chapter 1 Summary of NDA, (Item 3, Application Summary). The revision is identified using red strikeout for deletion and blue underline for revised information. Please note that the annotation for weight, has been revised from page 217 of the Chapter 6 Summary to Section 5.3 of the Integrated Summary of Efficacy, pages 33-35 (internal report number pages 31-33) and to the supporting data on page 96 (internal report number page 94) of Attachment 4 of the ISE. Attachment 4 is titled, "Prognostic Factors Statistical Output".
- **Attachment 4:** A revised NDA Chapter 6 Summary. The revision on page 12, paragraph two, is highlighted under the heading, "Overall Summary".

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

Desk copy to Jennifer Mercier, DRUDP, HFD 580

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



07 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 21-241

(norgestimate and ethinyl estradiol)

Amendment to a Pending
Application:

Response to Request for Information

ORIG AMENDMENT

BC

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the . Reference is also made to the Chemistry Team Leader's Information Request Letter (IRL) that was received via facsimile on 24 May 2001. At this time we wish to provide the following information for the chemistry reviewer. The FDA request as per the IRL, is presented below in bold-face type followed by RWJPRI's response.

- 1. Please provide the information concerning the holding time (length, storage conditions, etc...) of the drug product before blister packaging.**

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- 2. Please provide the details of the sampling plan/procedure used for analytical testing of each drug product at release and at stability.**

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J

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

4 pages

J



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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



BB

01 JUN 2001

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 21-241

Tablets (norgestimate and
ethinyl estradiol)

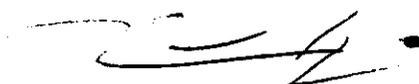
Amendment to a Pending
Application:
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the _____ . Reference is also made to Dr. Venkat Jarugula's 24 May 2001 and 31 May request to provide additional information. At this time we wish to provide the following the SAS transport file, _____ on diskette as per his telephone request today.

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	
ACTION:	
LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
BY INITIALS	DATE

Desk copy of diskette to Dr. Venkateswar Jarugula, PK Reviewer, HFD 580



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

AUG 25 2000

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 21-241 /
_____ Tablets
(norgestimate and ethinyl estradiol)

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 R.W. Johnson Pharmaceutical Research Institute (RWJPRI) is submitting a New Drug Application for _____ Tablets (norgestimate and ethinyl estradiol). _____ is a combination progestin/lower dose estrogen contraceptive indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a form of contraception. The following numbers were assigned to this application: NDA 21-241 and User Fee No. 3906. This application was prepared in accordance with 21 CFR 314.50 and applicable guidelines.

_____ is a combination progesterone/estrogen tablet taken orally once daily for 28 days. It is a triphasic regimen, which involves a stepwise increase in the dose of norgestimate from weeks 1 through 3 (0.180 mg, 0.215 mg, 0.250 mg). The ethinyl estradiol remains constant at 0.025 mg. Week 4 is a placebo tablet.

FDA Agreements

The following major agreements were reached at the Pre-NDA Meetings held 22 June 1999 and 04 October 1999 with members of the Division of Reproductive and Urologic Drug Products (DRUDP) and RWJPRI (Attachment 1):

- 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 Nonclinical Pharmacology and Toxicology, CM&C and Human Pharmacokinetics with respect to norgestimate and ethinyl estradiol.

- 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. However, the Division did recommend that we further support our pearl rate efficacy data in the Integrated Summary of Efficacy (ISE).
- 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) for Phase 2 studies. Phase 3 study data will be submitted electronically.
- No financial disclosure information will be provided in this application since all studies were completed on or before 02 February 1999.
- The Pediatric Labeling Requirement for the NDA contains the language previously provided for in Ortho's marketed oral contraceptives. A request for waiver can be found in Attachment 2 of this letter and Item 20 of the NDA.

In a subsequent agreement with the Division (see Attachment 3) we are providing in addition to paper copies, the following Items electronically on CD-ROMs:

Item 2	Draft Labels/Labeling
Item 3	Overall NDA Summary
Item 4	Chemistry, Manufacturing and Controls
Item 5	Nonclinical Pharmacology and Toxicology
Item 6	Human Pharmacokinetics and Bioavailability:
Item 8/10	Clinical/Statistical Data
Item 11	Case Report Tabulations (electronic only)
Item 12	Case Report Forms (electronic only)

For ease of review, the CD-ROM for each section will be 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). As agreed upon in Attachment 3, Item 11 includes Datalistings as ASCII format and Datasets as SAS Transport files. An index of the contents of the CD-ROMs is included in Attachment 4. All CD-ROMs have been scanned and deemed virus-free using McAfee VShield program version 4.0.3, scan engine version 4.070, virus definition 4.0.4091.

Physician's Package Insert/Patient Instructions

The draft Physician's Package Insert and Patient Instructions are identical to the currently marketed ORTHO CYCLEN/TRI-CYCLEN Labeling, except for the CMC information, human pharmacokinetics/bioavailability data and

As agreed upon with the FDA on 01 August 2000, any new or modified information will be italicized, underlined and annotated. Additionally, based on our discussions during the 22 June 1999 Pre-NDA meeting, we have chosen class labeling for our clinical section of the package insert as per the Labeling Guidance for Combination Oral Contraceptives (August 1994).

Demonstration of Safety and Efficacy

Pursuant to 505(b)(1) of the Act, the new safety and efficacy data for _____ is provided by seven clinical studies conducted by RWJPRI. This clinical program included four Phase 1, two Phase 2 and one Phase 3 studies to provide exposure to _____. Safety information was collected for 1,785 women who received _____ in the clinical investigations, including 1,723 subjects who received _____ in the pivotal Phase 3 study (NRGLOW-OC-001) for a planned duration of 6 or 13 cycles (total exposure, 11,062 treatment cycles). A total of 1,673 women provided 11,003 cycles of data with _____ for efficacy in the pivotal study; of these 274 women used _____ for 13 cycles.

As per the Division's suggestion during the Pre-NDA Meeting, we have further substantiated our pearl index efficacy data by reviewing and summarizing several summary basis of approvals for competitive oral contraceptive products. The summaries are located in the ISE Attachment 2.

Reviewers' 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 11) 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 section's content and organization and to facilitate locating documents contained therein.

Trademark

On 09 February 1999, the Labeling and Nomenclature Committee deemed our trademark _____ acceptable (see Attachment 5). Upon further consideration of general issues related to female health care products, it was determined that the trademark _____ would be more appropriate. On 10 April 2000, a letter was submitted to the division for a consult with the Office of Post-marketing Drug Risk Assessment (OPDRA) for our newly proposed name _____ (see Attachment 5). Throughout the NDA, the labeling, packaging components and all Reviewers' Guides contain the name _____. During development of this product, the designations, _____, _____, Low dose and _____ have been used in other documents of the NDA. All of these designations refer to the same drug product presented in this NDA.

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)

- CD-ROM of the Case Report Tabulations for the Phase 3 study (NRGLOW-OC-001) and all of the Case Report Forms for patients who died, discontinued due to an adverse event or became pregnant.

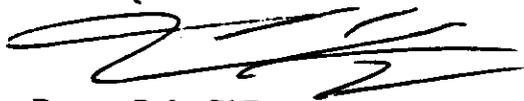
User Fee

The required User Fee of \$285,740.00 was submitted under separate cover to Mellon Bank, Pittsburgh, PA on 26 July 2000 (User Fee No. 3906). The required User Fee Cover Sheet (Form FDA 3397) is signed and included in this application in Item 18.

Should you have questions concerning this application, 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

Enclosures

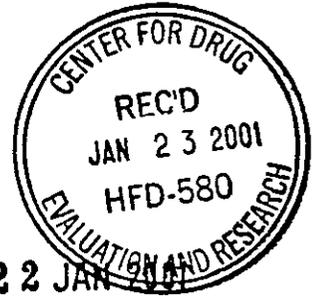
**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



ORIG AMENDMENT

BC

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 21-241

Tablets (norgestimate and
ethinyl estradiol)

Amendment to a Pending
Application:
Response to Request for
Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-241, submitted on 25 August 2000, for a combination progesterone/estrogen tablet for the [redacted]. Reference is also made to the Agency's 12 January 2001 request to provide additional information for the chemistry reviewer. At this time we wish to provide the following information.

CMC Table 4.1 Facilities Involved in Testing of Active Compounds:

At this time [redacted] the RW Johnson Research Institute [redacted]. Additionally, the address for [redacted] has been revised to reflect their testing facility address. The revised table is attached.

CMC Table 4.36 Facilities Involved in Testing, Labeling and Warehousing of Drug Product:

The address for [redacted] has been revised to reflect their testing facility address. As per your request attached is an updated table.

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 hope that you will find this information acceptable. 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.

See Chemistry [redacted] 2001

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Valerie A. Donnelly for /

Ramon Polo, PhD
Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW COMPLETED	
<input type="checkbox"/> LETTER	<input type="checkbox"/> FAX
<input type="checkbox"/> MEMO	<input type="checkbox"/> MEMO
CSO INITIALS	DATE

ORIGINAL



THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



11 MAY 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 21-241

(norgestimate/ ethinyl estradiol)

AMENDMENT TO A
PENDING APPLICATION
for Labeling Information

ORIG AMENDMENT

Dear Dr. Allen:

BL

Reference is made to our pending NDA 21-241 for ORTHO TRI-CYLCEN® Lo and to the draft package components submitted with the original application on 25 August 2000 NDA (Item 2, volume 1, page 44). We are amending NDA 21-241 with color copies of the proposed blister ring, foil over wrap and packer (front and back) for the finished drug product. The draft label enclosed is a 1:1 ratio text mock-up of the draft packaging components. This amendment is being provided at this time in order to provide color copies and to revise the packaging components to reflect the newly accepted trademark ORTHO TRI-CYCLEN® Lo. Four copies of each draft component are attached.

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,

Valerie A. Donnelly for /

Ramon Polo Ph.D.
Director
Regulatory Affairs

Enclosures (4)

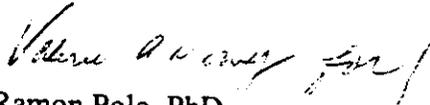
**APPEARS THIS WAY
ON ORIGINAL**

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

- Page 29, Reference List: We added the journal page numbers to Reference number 99.
- Page 36, INSTRUCTIONS FOR USING YOUR DIALPAK® TABLET DISPENSER: We revised the icons to include small boxes next to Sunday Start and Day 1 Start. We also capitalized the heading. This is consistent with ORTHO CYCLEN® and TRI-CYCLEN®. The text and icons did not change.
- Page 45: We have changed the words _____ to "healthcare professional" to be consistent with earlier sections of the label.
- Page 49, PREGNANCY DUE TO PILL FAILURE: In order to remain consistent with the language in an earlier section of the label, we copied text from page 29, Brief Summary Patient Package Insert-paragraph one, to page 49, Detailed Patient Labeling-paragraph one. We believe that this text provides more detailed information for the patient.

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

Send 1 desk copy to Jennifer Mercier, DRUDP, HFD 580

**APPEARS THIS WAY
ON ORIGINAL**

(K)

**Number of Pages
Redacted** 2



**Confidential,
Commercial Information**

K

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 U.S. Route # 202, P.O. Box 300
Raritan, New Jersey 08869-602

TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499

DATE: 05 October 2000

TO: JENNIFER MERCIER
Project Manager, FDA
Div. Reprod. & Urol. Drug Products

FROM: Valerie Donnelly
Regulatory Affairs
Phone: (908) 704-5891
Fax: (908) 203-1499

TELEFAX #: (301) 827-4267

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 3

NOTE: If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

MESSAGE (If any):

JENNIFER,
RE: NDA 21-241

AS PER THE DIVISION'S REQUEST ON OCTOBER 2, 2000, WE ARE PROVIDING THE CM&C LETTERS OF AUTHORIZATION FOR THE _____
IF YOU REQUIRE ADDITIONAL INFORMATION OR IF YOU HAVE QUESTIONS PLEASE CALL ME. THANK YOU

CONFIDENTIALITY NOTICE

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ON ORIGINAL

ASSIGNED INSPECTION 02-MAY-2001 PS VSTOAKES
 INSPECTION PERFORMED 01-JUN-2001 04-MAY-2001 VSTOAKES
 CTL PROFILE ACCEPTABLE. PLEASE NOTE THAT THIS SITE DID NOT CONDUCT ANY
 TESTING IN SUPPORT OF NDA 21241.
 DO RECOMMENDATION 01-JUN-2001 ACCEPTABLE VSTOAKES
 INSPECTION
 CTL PROFILE ACCEPTABLE BASED UPON 5/3/2001 INSPECTION. PLEASE NOTE THAT THIS
 LABORATORY DID NOT CONDUCT ANY TESTING IN SUPPORT OF NDA 21241.
 OC RECOMMENDATION 01-JUN-2001 ACCEPTABLE FERGUSONS
 DISTRICT RECOMMENDATION

Establishment: _____

DMF No: _____ AADA:
 Responsibilities: _____
 Profile: CSN OAI Status: NONE
 Estab. Comment: _____ (on 20-OCT-
 2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
ASSIGNED INSPECTION	30-OCT-2000	GMP			EGASM
SUBMITTED TO OC	11-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	16-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	22-FEB-2001		14-MAR-2001		IRIVERA
INSPECTION PERFORMED	16-MAR-2001		14-MAR-2001		EGASM
DO RECOMMENDATION	09-APR-2001			ACCEPTABLE INSPECTION	EGASM
BASED ON INVESTIGATOR'S COMMENTS, AND FIRM HISTORY					
OC RECOMMENDATION	09-APR-2001			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: _____

DMF No: _____ AADA:
 Responsibilities: _____
 Profile: CSN OAI Status: NONE
 Estab. Comment: _____ 20-OCT-2000 by J.
 BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
DO RECOMMENDATION	30-OCT-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 9/23/99					
OC RECOMMENDATION	30-OCT-2000			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: _____

APPEARS THIS WAY
ON ORIGINAL

DMF No: _____ AADA:
 Responsibilities: _____
 Profile: CSN OAI Status: NONE
 Estab. Comment: _____ (on 20-OCT-2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
DO RECOMMENDATION	30-OCT-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	30-OCT-2000		9/23/99	ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	11-JAN-2001				BOALJ
OC RECOMMENDATION	12-JAN-2001			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 2650104
 JANSSEN ORTHO INC
 STATE RD 933 KM 0.1 MAMEY WARD
 GURABO, PR 00658

DMF No: _____ AADA:
 Responsibilities: FINISHED DOSAGE MANUFACTURER
 Profile: TCM OAI Status: NONE
 Estab. Comment: MANUFACTURER OF PLACEBO TABLETS. (on 11-JAN-2001 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			FERGUSONS
DO RECOMMENDATION	12-JAN-2001			ACCEPTABLE BASED ON FILE REVIEW	MTORRES
OC RECOMMENDATION	12-JAN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: _____
 DMF No: _____ AADA:
 Responsibilities: _____
 Profile: CTL OAI Status: NONE
 Estab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
OC RECOMMENDATION	23-OCT-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: _____

APPEARS THIS WAY ON ORIGINAL

ORTHO BIOLOGICS INC
RD NUMBER 2 KM 46 BO CAMPO ALEGRE
MANATI, PR 00701

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
SUBMITTED TO DO	23-OCT-2000	GMP			DAMBROGIOJ
DO RECOMMENDATION	03-NOV-2000			ACCEPTABLE	MTORRES
OC RECOMMENDATION	06-NOV-2000			BASED ON FILE REVIEW ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 2211100

ORTHO PHARMACEUTICAL CORP
1000 RTE 202
RARITAN, NJ 08869

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE PACKAGER

Profile: TCM OAI Status: NONE
Estab. Comment: RELEASE AND STABILITY TEST OF DRUG SUBSTANCE. PACKAGING OF THE
BULK DRUG PRODUCT.
RELEASE AND STABILITY TESTING OF FINISHED DRUG PRODUCT. PACKAGING.
LABELING. (on 20-OCT-2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
OC RECOMMENDATION	23-OCT-2000			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: 2242831

ORTHO PHARMACEUTICAL CORP
NUMBER 1 CAMPUS DR
SOMERSET, NJ 08873

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
INTERMEDIATE STABILITY TESTER

Profile: CTL OAI Status: NONE
Estab. Comment: STORAGE AND SAMPLING OF DRUG SUBSTANCES AND EXCIPIENTS. (on 20-
OCT-2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	23-OCT-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	09-NOV-2000	PS			RBROWN4
DO RECOMMENDATION	23-FEB-2001			ACCEPTABLE	NROLI
				BASED ON FILE REVIEW	

THIS SITE SERVES AS ONLY A WAREHOUSE OF RAW MAERIALS AND FINISHED PRODUCT.
PRODUCT IS TESTED AT ORTHO IN RARITAN CFN # 2211100.

APPEARS THIS WAY
ON ORIGINAL

OC RECOMMENDATION 26-FEB-2001

ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment: 2650078

ORTHO PHARMACEUTICALS INC
BO CAMPO ALEGRE
MANATI, PR 00674

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE STABILITY TESTER

Profile: TCM

OAI Status: NONE

Estab. Comment: MANUFACTURER OF THE TABLETS. (on 20-OCT-2000
by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
SUBMITTED TO DO	23-OCT-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	03-NOV-2000			ACCEPTABLE	MTORRES
OC RECOMMENDATION	06-NOV-2000			BASED ON FILE REVIEW ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: _____

DMF No:

AADA:

Responsibilities: _____

Profile: CTL

OAI Status: NONE

Estab. Comment: _____ (on 12-
JAN-2001 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			FERGUSONS
DO RECOMMENDATION	01-FEB-2001			ACCEPTABLE	MFADDEN
				BASED ON FILE REVIEW	

OC RECOMMENDATION 02-FEB-2001

ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

Establishment: _____

DMF No:

AADA:

Responsibilities: _____

APPEARS TO BE
ON ORIGINAL

14-JUN-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Page 6 of 6

Profile: CTL OAI Status: NONE
Estab. Comment: _____ (on 12-JAN-2001 by J. BOAL (HFD-
580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-2001				BOALJ
OC RECOMMENDATION	12-JAN-2001		●●	ACCEPTABLE BASED ON PROFILE	FERGUSONS

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/s/

Jila Boal
6/21/01 03:32:54 PM
CHEMIST

Moo-Jhong Rhee
6/21/01 05:02:37 PM
CHEMIST
I concur

**APPEARS THIS WAY
ON ORIGINAL**

Filing Meeting Minutes

Date: July 25, 2002 **Time:** 11:00-12:00 PM **Location:** PKLN; 17B43

NDA 21-241 **Drug:** Ortho Tri-Cyclen Lo (norgestimate/ethinyl estradiol) Tablets

Indication: _____

Sponsor: Johnson & Johnson Pharmaceuticals

Type of Meeting: Filing

Meeting Chair: Scott Monroe, MD – Acting Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Jennifer Mercier - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Scott Monroe, M.D. – Acting Team Leader, DRUDP (HFD-580)

Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)

Venkat Jarugula, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Jennifer Mercier – Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish if the submission is fileable.

Background: Johnson & Johnson submitted a resubmission to their June 25, 2001 approvable action for their NDA.

Discussion/Decisions Made:

Clinical comments:

- This application is fileable.
- The medical officer will review the labeling for this product pending final review.

Clinical Pharmacology and Biopharmaceutics comments:

- This application is fileable.
- The biopharmaceutics reviewer will review the labeling for this product pending final review.

Statistical comments:

- No statistical review is needed for this resubmission.

Toxicology comments:

- No pharmacology review is needed for this resubmission.

Chemistry:

- No chemistry review is needed for this resubmission.

July 25, 2002
Filing Meeting Minutes
NDA 21-241
Page 2

Action Items:

- Make changes to the N drive for this label.
- Tradename consult has been sent to DMETS for final review.

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/s/

Scott Monroe
8/19/02 06:11:28 PM

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ON ORIGINAL**

Labeling Meeting Minutes

Date: June 13, 2001 **Time:** 9:00 – 10:00 AM **Location:** Parklawn; 17B-43

NDA 21-241 **Drug:** ORTHO TRI-CYCLEN Lo (norgestimate/ethinyl estradiol)

Indication: _____

Type Of Meeting: Labeling Status

Meeting Chair: Daniel Shames, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Daniel Shames, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Dena Hixon, M.D. – Team Leader, DRUDP (HFD-580)

Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)

Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Lisa Stockbridge, Ph.D. – Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-040)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Purpose of the Meeting:

To discuss the proposed label for this application.

Decisions Made:

See attached label.

Action Items:

- Send sponsor the label by June 14, 2001.(sponsor sent label 6.14.01)

Minutes Preparer

Minutes Concurrence

**APPEARS THIS WAY
ON ORIGINAL**

Drafted: June 18, 2001

Initialed: Rumble6.18.01/Shames6.18.01/Willett6.20.01

Final: June 21, 2001

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/s/

Daniel A. Shames
6/21/01 12:00:21 PM

**APPEARS THIS WAY
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Labeling Meeting Minutes

Date: June 6, 2001 **Time:** 10:30 – 11:30 AM **Location:** Parklawn; 17B-43

NDA 21-241 **Drug:** ORTHO TRI-CYCLEN Lo (norgestimate/ethinyl estradiol)

Indication: _____

Type Of Meeting: Labeling Status

Meeting Chair: Daniel Shames, M.D.

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Susan Allen, M.D., M.P.H. – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)

Dena Hixon, M.D. – Team Leader, DRUDP (HFD-580)

Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)

Jila Boal, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII; HFD-715)

Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Purpose of the Meeting:

To discuss the proposed label for this application.

Decisions Made:

See attached label for recommendations and revisions.

Biopharmaceutics:

- The Drug Interaction section of the label will be revised to reflect the review of the drug product.

Action Items:

- Send sponsor the revised label by June 14, 2001 (sponsor sent label 6.14.01).

Minutes Preparer

Minutes Concurrence

Drafted: June 18, 2001

Initialed: Rumble6.18.01/Ng6.20.01/Shames6.18.01/Allen6.18.01

Final: June 21, 2001

**APPEARS THIS WAY
ON ORIGINAL**

Status Meeting Minutes

Date: May 30, 2001 **Time:** 9:00 – 9:45 AM **Location:** Parklawn; 17B-43

NDA 21-241 **Drug:** ORTHO TRI-CYCLEN Lo (norgestimate/ethinyl estradiol)

Indication: _____

Type Of Meeting: 9 Month Status

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Chair: Daniel Shames, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:

Daniel Shames, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Dena Hixon, M.D. – Team Leader, DRUDP (HFD-580)

Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)

Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Jila Boal, Ph.D. – Chemistry Reviewer, Division of New Drug Chemistry II (DND CII) @ DRUDP (HFD-580)

Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII; HFD-715)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Purpose of the Meeting:

To discuss the review status and any labeling recommendations for this application.

Decisions Made:

Statistics:

- Review is pending.
- The sponsor needs to provide their definition of “cycle” in order to complete the calculations.

Clinical:

- This product has a higher Pearl Index (2.36%) compared to some other oral contraceptive products; however, this product did perform better than the approved comparator in the clinical trials
- This product also performed better than the comparator with regard to bleeding patterns, but the comparator has a poor bleeding pattern record
- The labeling will be revised with regard to these issues

Chemistry:

- The chemistry review is complete and a discipline review letter has been sent to the sponsor regarding the deficiencies noted in the review. (letter sent dated May 24, 2001)

Biopharmaceutics:

- The review is pending.
- With respect to the Drug-Drug Interaction section of the labeling, recommendations are forthcoming.

Action Items:

- Request sponsor to clarify their definition of "cycle" for the statistician.
- Request sponsor to submit an annotated label.
- All labeling comments should be made on the "N" drive.

Minutes Preparer

Minutes Concurrence

Drafted: April 25, 2001

Initialed:

Rumble6.7.01/Ng6.11.01/Willett6.11.01/Boal6.8.01/Jarugula6.7.01/Hixon6.14.01

Final: June 21, 2001

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/s/

Daniel A. Shames
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Number of Pages
Redacted 39



Draft Labeling
(not releasable)

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(M)

D/F

Meeting Minutes

Date: June 22, 1999 **Time:** 3:00-4:30 PM **Location:** Parklawn; Conference Room "C"

IND 11,391 **Drug:** Norgestimate/Ethinyl Estradiol **Indication:** 

Sponsor: R.W. Johnson

Type of Meeting: Pre-NDA

Meeting Chair: Lisa Rarick, M.D.

External Lead: George Creasy, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

**APPEARS THIS WAY
ON ORIGINAL**

FDA Attendees:

Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products; (DRUDP; HFD-580)

Marianne Mann, M.D. – Deputy Director, DRUDP (HFD-580)

Susan Allen, M.D. – Team Leader, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DND CII) @ DRUDP (HFD-580)

Jila Boal, Ph.D. – Chemist, DND CII @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, (OCPB) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Larry Abrams, Ph.D. – Research Fellow, Clinical Drug Metabolism, R.W. Johnson

Brandon Clark – Vice President, Global Franchise Leader, R.W. Johnson

George Creasy, M.D. – Director, Clinical Research Reproductive Health, R.W. Johnson

Alan Fisher, Dr.P.H. – Research Fellows, R.W. Johnson

Ceile Hedberg, D.V.M., Ph.D. – Global Project Director, R.W. Johnson

Patricia Johnson – Principal Regulatory Affairs Specialist, R.W. Johnson

Debakar Panigrahi, Ph.D. – Research Fellows, Drug Safety, R.W. Johnson

Ramon Polo, Ph.D. – Associate Director, Regulatory Affairs, R.W. Johnson

Gary Shangold, M.D. – Vice President, Regulatory Affairs, R.W. Johnson

Meeting Objective: To discuss and provide comment regarding the Pre-NDA meeting package that was submitted to the Division May 24, 1999.

Discussion:

Questions (Clinical)

1. Can comparative results from an RCT such as NRGLOW-OC-001, comparing an approved oral contraceptive to an investigational oral contraceptive, demonstrate the efficacy of the investigational regimen when the Pearl rate for the approved product is 3.29?
 - to date, this product has been studied in 6500 patients in four treatment groups; one treatment group was discontinued
 - differences between the Ortho-TriCyclen™ study design and this study should be explicitly stated in the NDA. Pregnancy rates were higher than expected in this study but the different study design may explain this; a literature search of recently approved products may also provide information to explain the higher than expected pregnancy rate; this is a review issue
 - Loestrin™ data from the past may not be comparable to current studies
 - the Pearl rates and life-table pregnancy rates should be broken down by "perfect" use (if possible). There would be no superiority claim for efficacy for this application
2. If comparative data from an RCT is accepted as proof of efficacy for an investigational regimen, even when the approved product comparator has a study Pearl of 3.29, would the labeled description of efficacy be the same for the investigational product as for the approved product?
 - this is a review issue
 - the label might need to reflect the actual results from the study, but discussions about labeling will occur during the NDA review
3. ISS and ISE proposals
 - the ISS and ISE proposals are acceptable
4. Financial Disclosure
 - since no clinical studies supporting this NDA were conducted or ongoing as of February 2, 1999, the proposed financial disclosure section is acceptable

Human Pharmacokinetics

1. Population Pharmacokinetics proposal
 - the proposal is acceptable
 - the sponsor does not have the absorption rate and clearance available at this time
2. Food Effects Bioavailability Studies proposal
 - food effect studies suggested, but are not a requirement
 - if the food-effects study is conducted, the data will be included as part of the label

3. Literature Review (drug-drug interaction) proposal

- this proposal is acceptable to the Division
- information on metabolism should also be included

4. Waiver of Bioavailability

- this proposal is acceptable to the Division
- dissolution testing will be done for the color change in the product and data will be provided in the NDA

5. Overall, does the Division agree that the proposed Biopharmaceuticals plan is sufficient to support the Phase 3 pivotal study and a future NDA submission for the NGM/EE tablet investigational product?

- the proposal appears to be adequate

Nonclinical

1. The primary Pharmacology, Toxicology and ADME data will be cross-referenced to ORTHO-CYCLEN (NDA 19-653)

- this proposal is acceptable to the Division

2. New data generated for the NGM/EE Tablet investigational formulation program includes single and multiple dose rat, rabbit, and monkey absorption and pharmacokinetic studies conducted with NGM and 17-deactylnorgestimate (a primary metabolite of norgestimate). It will also include *in vitro* and *in vivo* metabolism studies in the rat and rabbit as well as two protein-binding studies in female subjects. Does the agency agree that sufficient nonclinical data are available to support an NDA for this program?

- this proposal is acceptable to the Division

NDA Format

1. Item 11: Tabulations

- this proposal is acceptable to the Division

2. Item 10: Statistical Section

- this proposal is acceptable to the Division

3. Electronic NDA submission:

- additional details can be discussed after this Pre-NDA meeting
- because the data is cross-referenced to Ortho-Cyclen (NDA 19-653), if information is not located easily, DRUDP may request that the information be submitted directly to the NDA,
- the reports will be summarized in the new NDA and actual reports will be available in the previously submitted NDA

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IND

Meeting Minutes

Page 4

4. CANDA Proposals

- SAS data sets are acceptable to the Division

Unresolved decisions: None

Action Items:

- Meeting minutes to the sponsor within 30 days

JSI
Minutes Preparer

JSI
Concurrence, Chair

cc:

Original IND

HFD-580/DivFile

HFD-580/Rumble6.28.99/Mercier

HFD-580/Rarick6.29.99/Mann/Allen/Slaughter/Price/Bennett/Rhee/Lin/Jordan/Raheja/

Parekh/Jarugula/Kammerman/Boal

drafted: June 24, 1999/Mercier

concurrence: Rumble6.28.99/Rarick6.29.99/Allen7.6.99/Lin7.2.99/Mann7.1.99/Boal6.30.99

Kammerman6.30.99/Bennett6.30.99

final: July 7, 1999

MEETING MINUTES

**APPEARS THIS WAY
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Kish

Meeting Minutes

Date: October 29, 1997 **Time:** 11:45 AM - 12:30 PM **Location:** Parklawn 17B-43

IND 11,391 **Drug Name:** norgestimate (NGM) and ethinyl estradiol (EE) tablets

External Participant: R.W. Johnson

Type of Meeting: Pre-NDA CMC and Biopharmaceutics

Meeting Chair: Heidi Jolson, M.D., M.P.H.

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ON ORIGINAL**

External Participant Lead: Patti Johnson

Meeting Recorder: Christina Kish

FDA Attendees:

Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Vanketeswar Jarugula, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Tatiana Pavlova, M.D. - FDA Fellow @ DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

Larry Abrams, Ph.D. - Research Fellow, Clinical Drug Metabolism

Carolyn Campen, Ph.D. - Associate Director, Global Research and Development

Joseph Etse, Ph.D., Principal Scientist, Analytical Development

David Goldberger, M.S., R.Ph. - Manger, Regulatory Affairs

Angela Falzone, Ph.D. - Principal Scientist, Process Development Technical Services

Hsiao Guh, Ph.D. - Research Manager, Pharmaceutical Development

Patricia Johnson - Senior Associate, Regulatory Affairs

Meeting Objectives:

To gain concurrence regarding the Chemistry Manufacturing and Controls (CMC) and Biopharmaceutic portions of their upcoming NDA submission for this oral contraceptive.

Discussion Points:

- General

•

•

- a clinical pre-NDA meeting will be requested mid-1998

- Biopharmaceutics
 - the sponsor will cross reference the NDA's of their already approved products Ortho-Cyclen and Ortho Tricyclen to support some of the biopharmaceutic study requirements
 - the sponsor's proposed biopharmaceutic trials (see attached) are acceptable
 - the sponsor was reminded that protocols could be submitted in draft prior to initiation of those studies if Division comments were desired
 - the Division suggested that a food-effects study be performed for both estradiol and norgestimate, however this is not a required study
 - the Division suggested the sponsor perform or submit P450 metabolic data for norgestimate
 - any literature regarding drug interactions with the components of this product should be submitted with the applications

- Chemistry Manufacturing and Control (CMC)
 - the sponsor's proposal for the timing of submissions of stability data and their stability program (see attached) are acceptable
 - the sponsor should examine drug substance aggregation during their normal retest time points in the stability studies
 - ~~_____~~
 - ~~_____~~
 - the sponsor must provide three method validation packages for each application
 - the sponsor may provide methods validation samples and data for the new methods and formulations only
 - the drug substance assay must be submitted
 - the drug product assay must be provided with validation
 - technical summaries in Microsoft 7.0 will be provided however batch records will not be available electronically; a full hardcopy of the CMC submission will be provided
 - the sponsor's proposed format of the CMC section of the to-be-submitted applications is acceptable
 - the sponsor must provide a rationale including documentation for the ~~_____~~ overage found in the drug substance
 - the sponsor was advised that a dissolution profile must, at a minimum, provide for ~~_____~~ dissolution at a to-be-specified by sponsor time point; a ~~_____~~ dissolution rate is not considered acceptable
 - the sponsor was requested to place all manufacturing sites in a single sub-section of the CMC section of the upcoming submission

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(N)

The. R. W. Johnson Pharmaceutical Research Institute

IND 11,391

**Investigational Norgestimate/Ethinyl Estradiol
Tablet Formulation**

October 29, 1997

Pre-NDA Meeting: Chemistry, Manufacturing and Controls

End of Phase 2 Meeting: Human Pharmacokinetics

**APPEARS THIS WAY
ON ORIGINAL**

AGENDA

Pre-NDA Meeting: Chemistry, Manufacturing and Controls
End of Phase 2 Meeting: Human Pharmacokinetics

October 29, 1997

- | | | |
|------------------|---|---------------------|
| 11:15 - 11:20 AM | Introduction/Overview | Patricia M. Johnson |
| 11:20 - 11:30 AM | Summary: Chemistry, Manufacturing
and Controls | Joseph Etse |
| 11:30 - 11:40 AM | Summary: Human Pharmacokinetics | Larry Abrams |
| 11:40 - 1:15 PM | Discussion of Issues/Questions for FDA | All attendees |

**APPEARS THIS WAY
ON ORIGINAL**

IND 11,391

**Investigational Norgestimate/Ethinyl Estradiol
Tablet Formulation**

January 8, 1997	End of Phase 2 Meeting: Clinical Overview <ul style="list-style-type: none">• K90-023 (Phase 2 Study)• N93-031 (Phase 2 Study)• NRGLOW-OC-001 (proposed Phase 3 Protocol)
February 5, 1997	NRGLOW-OC-001 revised and submitted for comment (serial no. 086)
March 25, 1997	Phase 3 Study NRGLOW-OC-001 submitted to IND (serial no. 087)
July 7, 1997	Received comments on NRGLOW-OC-001
September 15, 1997	Revised NRGLOW-OC-001 revised and submitted (serial no. 104): statistical analysis plan revised

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RELEASABLE**

15 pages

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Advisory Committee
N/A

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8/21/09

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYLEN® Lo

norgestimate/ethinyl estradiol

3S

R. W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier

HFD-580

7-4260

Advisory Committee

N/A

APPEARS THIS WAY
ON ORIGINAL

JSM
6/14/01

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

FR Notice
N/A

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8/21/02

APPEARS THIS WAY
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NDA 21-241

ORTHO TRI-CYLEN® Lo

norgestimate/ethinyl estradiol

3S

R. W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier

HFD-580

7-4260

FR Notice

N/A

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ON ORIGINAL**

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JSI
6/14/01

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA NDA 21-241
Applicant Johnson and Johnson Pharmaceutical Research & Development, L.L.C.
Type of Application Complete response to approvable action
Proprietary Drug Name Ortho Tri-Cyclen® Lo
Generic Drug Name Norgestimate/ethinyl estradiol
Doses of Drug 180 µg norgestimate + 25 µg ethinyl estradiol (days 1-7)
215 µg norgestimate + 25 µg ethinyl estradiol (days 8-14)
250 µg norgestimate + 25 µg ethinyl estradiol (days 15-21)
placebo (days 22-28)
Indication _____
Date of Submission June 25, 2002
Date of Memorandum August 22, 2002
Reviewer Scott E Monroe, MD
Acting Clinical Team Leader, DRUDP

SUMMARY

Ortho Tri-Cyclen® Lo is a triphasic oral contraceptive containing norgestimate and ethinyl estradiol. The doses of norgestimate (180 µg on days 1-7, 215 µg on days 8-14, and 250 µg on days 15-21) are identical to those in the Applicant's approved product Ortho Tri-Cyclen®; the daily dose of 25 µg ethinyl estradiol on days 1-21 in Ortho Tri-Cyclen® Lo is lower than the 35 µg dose in Ortho Tri-Cyclen®.

Approval of Ortho Tri-Cyclen® Lo for marketing as a combination oral contraceptive in the United States is recommended based on the data presented in the original NDA submitted on August 25, 2000, the Applicant's complete response of June 25, 2002, and final revised labeling submitted on August 19, 2002.

BACKGROUND

This sponsor currently markets two approved combination oral contraceptives containing norgestimate and ethinyl estradiol. Ortho Cyclen® is a monophasic combination oral contraceptive containing 250 µg of norgestimate and 35 µg of ethinyl estradiol that is administered for 21 days followed by placebo for 7 days. Ortho Tri-Cyclen® is a triphasic combination oral contraceptive providing a stepwise increase in norgestimate (180 µg on days 1-7, 215 µg on days 8-14, and 250 µg on days 15-21) and a continuous dose of 35 µg of ethinyl estradiol that is administered for 21 days followed by placebo for 7 days. In Ortho Tri-Cyclen® Lo, the daily dose of ethinyl estradiol has been reduced

from 35 µg to 25 µg. The daily dose of norgestimate is identical to that in Ortho Tri-Cyclen®.

The original NDA for Ortho Tri-Cyclen® Lo was submitted in August 2000. Review of the application did not identify any safety concerns. There was, however, some concern about the efficacy of Ortho Tri-Cyclen® Lo based on the outcome of the single pivotal Phase III clinical trial. In this trial, 1,673 evaluable women received Ortho Tri-Cyclen® Lo for up to 13 cycles for a total of 11,003 treatment cycles. There were 14 pregnancies due to method failure and 6 pregnancies due to user failure. The "perfect use" (method failure) Pearl Index (PI) for pregnancy was 1.65 pregnancies per 100 women-years of use, and the "typical use" (method failure plus user failure) PI was 2.36 pregnancies per 100 women-years of use. In the Loestrin® Fe 1/20 comparator group (7,497 treatment cycles), there were 17 pregnancies due to method failure and 2 pregnancies due to user failure. The "perfect use" PI and the "typical use" PI were 2.95 and 3.29 pregnancies per 100 women-years of use, respectively.

Although the PI for Ortho Tri-Cyclen® Lo was somewhat higher than those for several recently approved hormonal contraceptive products, it was not higher than that for the approved comparator (Loestrin® Fe 1/20) and was within the published range of effectiveness for "typical use" of oral contraceptives. Based on these considerations, the Division of Reproductive and Urologic Drug Products (DRUDP) decided that Ortho Tri-Cyclen® Lo could be approved for marketing in the United States subject to inclusion of the PI in the drug label. The Applicant, however, did not agree to include the PI in the drug label, and the NDA received an approvable action, pending resolution of this issue.

PRESENT SUBMISSION (COMPLETE RESPONSE TO APPROVABLE LETTER)

In the present submission, the Applicant has provided a revised drug label and a safety update.

Revised Label

The revised label contains the requested information regarding the PI (2.36) for "typical use" for Ortho Tri-Cyclen® Lo based on the pivotal clinical trial. The following statement regarding efficacy has been added:



Medical Officer's Comment

- *The added information adequately addresses DRUDP's request to include efficacy information from the pivotal trial in the drug label.*

Safety Update

The safety update consisted of the following statement by the Applicant:

"All studies were completed as of 10 July 1998 and all safety data was included in the original NDA. We performed a database search for the period 25 June 2001 to 12 June 2002. No serious related adverse events were reported to Drug Safety and Surveillance for the product, ORTHO TRI-CYCLEN® Lo."

Medical Officer's Comment

- *There are no outstanding safety issues.*

Proprietary Drug Name

During the review of the original NDA, the Office of Postmarketing Risk Assessment (OPDRA) had found the trade name Ortho Tri-Cyclen® Lo unacceptable because prescribers might forget to write "Lo" when prescribing the product, or dispensing errors might occur because of the likelihood of storing the product on pharmacy shelves next to the similar product Ortho Tri-Cyclen®. OPDRA recommended ' _____' instead, but the sponsor declined to make this change. The review Division (DRUDP) did not believe at that time that the proposed name would propose a safety risk and therefore approved its use.

During the present review cycle, the Division of Medication Errors and Technical Support (DMETS) was consulted to review again the proposed proprietary name, Ortho Tri-Cyclen® Lo to ensure that there were no other proprietary or established names that had the potential for confusion with the proposed name. None were identified. However, DMETS also expressed concern about the placement of the designation of "Lo" at the end of the name instead of at the beginning.

Medical Officer's Comment

- *The review Division (DRUDP) continues to believe that the proposed name does not pose a safety risk and therefore approves the use of Ortho Tri-Cyclen® Lo.*

RECOMMENDED PHASE IV COMMITMENTS

No Phase IV commitments are needed.

CONCLUSIONS AND RECOMMENDATIONS

The Applicant has adequately addressed all of the unresolved issues in the approvable letter of June 25, 2001. Revised labeling submitted on August 19, 2002 is acceptable. There are no outstanding safety issues. Approval of Ortho Tri-Cyclen® Lo as a combination oral contraceptive for marketing in the United States is recommended.

Scott E. Monroe MD
Acting Clinical Team Leader/DRUDP

Daniel Shames, MD
Director/DRUDP

**APPEARS THIS WAY
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Cc: HFD-580/D. Shames/S. Monroe/G. Willett

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/s/

Scott Monroe
8/22/02 02:11:23 PM
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Daniel A. Shames
8/22/02 02:14:05 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

**GROUP LEADER MEMORANDUM
NDA 21-241**

Drug Ortho Tri-Cyclen® Lo

Generic Drug Name norgestimate/ethinyl estradiol

Dose 180 µg norgestimate + 25 µg ethinyl estradiol days 1-7
215 µg norgestimate + 25 µg ethinyl estradiol days 8-14
250 µg norgestimate + 25 µg ethinyl estradiol days 15-21
placebo days 22-28

Indication _____

Applicant The R.W. Johnson Pharmaceutical Research Institute

Date of Submission August 25, 2000

Date of Memorandum June 25, 2001

Reviewer Dena R. Hixon, M.D., FACOG
Team Leader, DRUDP

Summary

Ortho Tri-Cyclen® Lo is a triphasic oral contraceptive containing norgestimate and ethinyl estradiol (EE). The doses of norgestimate (180 µg on days 1-7, 215 µg on days 8-14, and 250 µg on days 15-21) are identical to those in the sponsor's approved product Ortho Tri-Cyclen®, and the daily dose of 25 µg ethinyl estradiol on days 1-21 is lower than the 35 µg dose in Ortho Tri-Cyclen®.

The data presented in this NDA is sufficient to support approval of Ortho Tri-Cyclen® Lo for marketing as a combination oral contraceptive in the United States.

Background

This sponsor currently markets two approved oral contraceptives containing norgestimate and ethinyl estradiol. Ortho Cyclen® is a monophasic combination oral contraceptive containing 250 µg of norgestimate and 35 µg of ethinyl estradiol to be administered for 21 days followed by placebo for 7 days. Ortho Tri-Cyclen® is a triphasic combination oral contraceptive providing a stepwise increase in norgestimate (180 µg on days 1-7, 215 µg on days 8-14, and 250 µg on days 15-21) and a continuous dose of ethinyl estradiol 35 µg to be administered for 21 days followed by placebo for 7 days.

Ortho Tri-Cyclen® is also indicated for treatment of moderate acne in females at least 15 years old who desire OCs for contraception and are unresponsive to topical acne medications. The sales volume for Ortho Tri-Cyclen® is higher than that of any other oral contraceptive. The efficacy and safety of Ortho Cyclen® and Ortho Tri-Cyclen® are similar to other marketed combination oral contraceptives.

The sponsor proposes that reduction of the estrogen dose in Ortho Tri-Cyclen® Lo may reduce the risk of venous thromboembolic events associated with the estrogen component in combination oral contraceptives. Preliminary phase 2 clinical trials revealed similar ovulation suppression and bleeding patterns for Ortho Tri-Cyclen® Lo and Ortho Tri-Cyclen®.

Reviewer's comment

The sponsor's assertion that the reduction of the estrogen dose may reduce the risks associated with the estrogen component of combination oral contraceptives is a logical justification for this product. Although the clinical studies do not show a lower incidence of typical estrogen-related side effects than was previously reported in the Ortho Tri-Cyclen® trials, these trials are not large enough to demonstrate a reduction in the less common serious risks associated with estrogen administration. Some women with individual risk factors, including women 40 years of age and older, might benefit from this lower dose formulation despite a slight reduction in efficacy.

Loestrin® Fe 1/20 was chosen for the active comparator for the pivotal clinical trial because it was the only available combined oral contraceptive with less than 30 µg of ethinyl estradiol at the time the study was planned.

Reviewer's comment

The choice of Loestrin® Fe 1/20 as an approved low dose oral contraceptive comparator for this study was appropriate, as the Pearl Index for pregnancies with Loestrin® Fe 1/20 in the phase 3 trials supporting its approval was less than 1.0, and there was no other approved oral contraceptive with less than 30 µg of EE at the time of initiation of the phase 3 trials for Ortho Tri-Cyclen® Lo.

Efficacy of Ortho Tri-Cyclen® Lo

The efficacy of Ortho Tri-Cyclen® Lo was supported by a single Phase III clinical trial and two dose-ranging/supportive efficacy studies. The phase 3 trial included 1,673 evaluable women who received Ortho Tri-Cyclen® Lo for up to 13 cycles. There were 1,351 Ortho Tri-Cyclen® Lo users under 35 years of age, with a total of 8,773 cycles of use. An additional 321 subjects age 35 and older completed 2,224 cycles of use. Two hundred twenty-one subjects age 35 and younger completed 13 cycles of Ortho Tri-Cyclen® Lo use, and 820 subjects age 35 and younger completed 6 cycles of use.

In the pivotal trial, there were 14 pregnancies due to method failure and 6 pregnancies due to user failure for a total of 20 pregnancies in Ortho Tri-Cyclen® Lo users. The "perfect use" (method failure) Pearl Index (PI) for pregnancy was 1.65 pregnancies per

100 women-years of use. The "typical use" (method failure plus user failure) PI was 2.36. In women below age 35, the "perfect use" PI for pregnancy was 1.78 and the "typical use" PI was 2.67.

In comparison, 1,141 women used the comparator product, Loestrin® Fe 1/20, for a total of 7,497 cycles (576.7 women-years). There were 17 pregnancies due to method failure and 2 pregnancies due to user failure in this group, giving a "perfect use" PI of 2.95 and a "typical use" PI of 3.29. For women below 35 years of age, the "perfect use" PI was 3.38 and the "typical use" PI was 3.80.

Reviewer's comment

1. *The "perfect use" PI pregnancy rates seen in this trial are higher than the "perfect use" pregnancy rates for combination oral contraceptives published in Contraceptive Technology and included in class labeling of contraceptive products. However, the overall ("typical use") pregnancy rates for Ortho Tri-Cyclen® Lo are within the published range for "typical use". Several other combination oral contraceptives have previously been approved with similar or slightly higher pregnancy rates. In addition, although this study was not powered a priori for comparative claims, use of Ortho Tri-Cyclen® Lo resulted in lower pregnancy rates than those seen with use of the approved comparator oral contraceptive Loestrin® Fe 1/20.*
2. *As noted by the primary reviewer, the sponsor's comments regarding historical differences in study design appear to be a valid explanation for the higher PI for Loestrin® Fe 1/20 in the pivotal study for this product compared to the lower PI for Loestrin® Fe 1/20 at the time of its approval. Other oral contraceptives have been approved based on studies in which the investigational product and the comparator product (previously approved oral contraceptives) were noted to have typical use PIs > 2 but well within the range of typical use PIs seen post-approval with marketed products*
3. *The primary reviewer has presented historical information regarding approved products with higher PI than that reported for Ortho Tri-Cyclen® Lo in the pivotal trial. These include PI of 2.4 for Estrostep®, 2.6 for Tri-Norinyl®, 5.18 for Brevicon®, and 2.51 for Norinyl®. The PI for Tri-Norinyl®, Brevicon®, and Norinyl® were calculated from a 4-cycle study conducted for the approval of Tri-Norinyl®, comparing bleeding patterns with Tri-Norinyl® use with those seen with the use of the already approved products Brevicon® and Norinyl®.*
4. *19% of participants in this trial were 35 years of age or older. Inclusion of these women may have introduced a bias in favor of lower pregnancy rates. In fact the PI was slightly higher (although not statistically significant) in the subset of women below age 35 (1.78 for "perfect use" and 2.67 for "typical use") than in the overall study population (1.65 for "perfect use" and 2.36 for "typical use"). This finding of a higher PI for women age 35 years or younger vs. women older than 35 years has also been noted in subanalyses of other approved oral contraceptives.*

Fertility is known to decline with age, especially after the age of 35 years. Therefore, efficacy evaluation of oral contraceptives should rely upon data obtained from women no older than 35 years. However, pregnancies do occur in older women, and it is therefore appropriate for them to be included in clinical trials so as to collect appropriate safety data for the entire range of women who may use the product when marketed.

- 4. The Division has been consistent in requiring a minimum exposure of 10,000 cycles of product use and at least 200 women completing 13 cycles of use to demonstrate efficacy of new hormonal contraceptive products. Recently, the Division also recommended modifications in trial designs for contraceptive products under development that will facilitate and standardize efficacy assessments for these products (i.e., requiring pregnancy testing at regularly scheduled intervals throughout these trials and at early discontinuation or trial completion, appropriate follow-up of pregnancies diagnosed during or shortly after the studies, and standardization of pregnancy assessment methods). Such recommendations were not consistently applied during development of many previously approved products.*
- 5. The primary reviewer recommended that the Division consider a limit for Pearl Index of pregnancies that could be accepted for future contraceptive product applications. While consideration could be given to establishing such limits, to do so would be useful only if every trial was conducted in an identical manner with an identical design. It is not clear that this is feasible given the frequent advances in technology that could require flexibility in trial design.*

Bleeding Patterns

Intermenstrual bleeding during Cycle 3 was reported by 23.6% of Ortho Tri-Cyclen® Lo users and 37.2% of Loestrin® Fe 1/20 users. The average duration of menses was longer in Ortho Tri-Cyclen® Lo users (5.4 days) than in Loestrin® Fe 1/20 users (4.4 days). Withdrawal flow was absent in 4.3% of Ortho Tri-Cyclen® Lo cycles and 19.6 % of Loestrin® Fe 1/20 cycles.

Further information requested from the sponsor revealed that 15% of subjects in both treatment groups experienced more than 7 total days of bleeding and/or spotting in cycle 3. Although the trial was not designed to show superiority in this regard, the proportion of women with more than 7 days of bleeding was higher with Ortho Tri-Cyclen® Lo use than with Loestrin® Fe 1/20 use in all cycles after cycle 3. In cycle 12, twelve percent of Ortho Tri-Cyclen® Lo users and 8% of Loestrin® Fe 1/20 users reported more than 7 days of bleeding and/or spotting.

Reviewer's comment

The incidence of intermenstrual bleeding at Cycle 3 was the sponsor's designated primary endpoint for evaluation of bleeding patterns. The reported 23.6% of Ortho Tri-Cyclen® Lo users with intermenstrual bleeding at Cycle 3 is higher than the incidence

reported in trials of other recently approved oral contraceptives (14% for Yasmin™, containing 30 µg of EE, and 17% for Cyclessa, containing 25 µg EE). However, comparisons across trials are problematic and do not permit definitive conclusions to be drawn regarding differences in bleeding patterns seen with use of different products.

More breakthrough bleeding and spotting is to be expected with use of lower estrogen doses. While most women would prefer predictable short menstrual periods with light flow and no spotting or bleeding between menstrual periods, intermenstrual bleeding is essentially a nuisance and not a significant safety concern. There was no evidence of anemia or serious adverse events related to bleeding in the clinical trial.

Safety and Tolerance of Ortho Tri-Cyclen® Lo

Of the 12 SAEs reported in Ortho Tri-Cyclen® Lo users in the pivotal trial, only one case of gall bladder symptoms in a woman with a prior history of gallstones and one case of major depression and personality disorder could possibly be related to the study drug.

Hypertension was reported in 0.7% of Ortho Tri-Cyclen® Lo users and in 0.4% of Loestrin® Fe 1/20 users. Only one subject in the Ortho Tri-Cyclen® Lo group had "marked" hypertension, and no subject reported hypertension as an SAE in the pivotal trial. One patient in phase 2 trials did report hypertension as an AE. However, her maximum reported blood pressure was 144/92, and was 136/70 at follow-up after discontinuation of the medication.

Weight gain was reported by 2.4% of Ortho Tri-Cyclen® Lo users and 2.1% of Loestrin® Fe 1/20 users.

There were no cases of DVT or PE in the pivotal trial. Two Ortho Tri-Cyclen® Lo users and one Loestrin® Fe 1/20 user had mild to moderate superficial phlebitis.

The incidence of depression was similar in both treatment groups (3.3% of Ortho Tri-Cyclen® Lo users and 3.4% of Loestrin® Fe 1/20 users). Only one Ortho Tri-Cyclen® Lo user reported depression as a serious AE.

Reviewer's comment

Ortho Tri-Cyclen® Lo differs from the widely used Ortho Tri-Cyclen® only in a lower dose of ethinyl estradiol, and the adverse events reported in the clinical trials are similar to those of other combination oral contraceptives. No new safety concerns have been identified with this product.

Clinical Assessment and Recommendations

I agree with the primary reviewer's recommendation that this product be approved with labeling that clearly shows the pregnancy rates reported in the pivotal trial.

Non-Clinical Assessments

Pharmacotoxicology

This product consists of two previously approved drugs with a lower dose of the estrogen component. The pharmacotoxicology team leader identified no safety issues. I agree with his recommendation for approval.

Chemistry, CDRH, and Microbiology

An Information Request letter was sent to the sponsor to resolve several issues identified in the primary chemistry review. The sponsor's response adequately addressed all of the issues. I agree with the recommendation of the chemistry review team for approval of this product.

Clinical Pharmacology

The primary biopharmaceutics reviewer found the NDA acceptable from Clinical Pharmacology and Biopharmaceutics perspective. A decrease in PK parameters was found in association with increasing body weight and with increasing age. However, there was no increase in pregnancies observed with increases in either body weight or age. I agree with the recommendation of the biopharmaceutics review team for approval with the recommended labeling changes.

DSI

No DSI inspection was performed because this is a new lower dose of an approved product, and the clinical reviewer did not identify any reason for concern about data integrity.

Tradename

The sponsor originally proposed the tradename _____ and both OPDRA and DRUDP found that name unacceptable because of confusion about the meaning of the suffix — which could be interpreted to be the number of pills in the cycle or the dose of either one of the components. OPDRA also found the current tradename Ortho Tri-Cyclen® Lo unacceptable because prescribers might forget to write "Lo" when prescribing the product, or dispensing errors might occur because of the likelihood of storing the product on pharmacy shelves next to the similar product Ortho Tri-Cyclen®. OPDRA recommended _____ instead, and the sponsor declined. OPDRA has acknowledged that the suffix "Lo" is appropriate to distinguish this product from Ortho Tri-Cyclen® because it does contain a lower amount of ethinyl estradiol. The review Division does not believe that the proposed name would propose a safety risk and therefore approves its use.

Facilities Inspection

All sites are satisfactory.

Phase IV commitment

No Phase IV commitments are needed.

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Labeling

As recommended by the clinical reviewer, the sponsor was asked to include the PI for pregnancies from the pivotal trial in the label. Recommendations for labeling revisions from all disciplines were provided to the sponsor on 6/14/01. The sponsor was not able to reach agreement with the Division regarding appropriate labeling, and therefore the application is found approvable pending agreement on acceptable labeling.

Conclusions and Recommendations

This application is approvable pending future agreement on acceptable labeling.

**APPEARS THIS WAY
ON ORIGINAL**

**Dena R. Hixon, M.D., FACOG
Team Leader/DRUDP**

**Daniel Shames, M.D., FACS
Deputy Director/DRUDP**

Cc: HFD-580/S. Allen/D. Shames/D. Hixon/G. Willett

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/s/

Dena Hixon
6/25/01 05:05:00 PM
MEDICAL OFFICER

Daniel A. Shames
6/25/01 05:11:49 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA: 21241 (Complete Response to an Action Letter)

Received: June 25, 2002

Sponsor: R.W. Johnson Pharmaceutical Research Institute

Proprietary Name: Ortho Tri-Cyclen® Lo

Medical officer review:

Ortho Tri-Cyclen® Lo is a combination oral contraceptive that contains norgestimate and ethinyl estradiol (EE). The level of ethinyl estradiol in Ortho Tri-Cyclen® Lo is less than that found in the previously approved Ortho Tri-Cyclen® (0.025 mg EE versus 0.035mg EE respectively). The norgestimate levels remain the same.

The sponsor received an approvable action on initial NDA review primarily because of labeling issues regarding the pregnancy rate observed with Ortho Tri-Cyclen® Lo. The agency requested that the sponsor include in the label the pregnancy rate observed in the Ortho Tri-Cyclen® Lo clinical trials. The pregnancy rate was 2.36 per 100 women years of use. The sponsor has agreed to include this rate in the label.

The sponsor has also accepted the full Trussell Table for inclusion in the label, but wishes to specify that Ortho Tri-Cyclen® Lo has not been studied for and is not indicated for use . This labeling comment regarding emergency contraception is acceptable.

A number of minor wording changes that were requested previously for Ortho-Cyclen® and Ortho Tri-Cyclen® were incorporated into the label for Ortho Tri-Cyclen® Lo.

This submission to the NDA also provided a safety update. All studies were completed as of 10 July 1998 and all safety data was included in the original NDA. A database search for the period 25 June 2001 to 12 June 2002 did not reveal any additional safety concerns.

Additional comment from the Office of Drug Safety (Aug 16, 2002) expressed concern about the proprietary name Ortho Tri-Cyclen Lo in regard to prescribers leaving off "Lo" or confusing it with PO. This reviewer does not feel that the proposed proprietary name presents a safety concern.

Recommendation: With resolution of labeling issues, an approval is recommended.

Gerald Willett, MD DRUDP
Cc: Shames, D; Monroe S

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/s/

Gerald Willett
8/21/02 03:35:04 PM
MEDICAL OFFICER

Scott Monroe
8/22/02 01:27:18 PM
MEDICAL OFFICER
I concur.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Safety Update
See Medical Officer review dated 8-21-02.

✓
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8/21/02

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYCLEN® Lo

norgestimate/ethinyl estradiol

3S

R.W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier

HFD-580

7-4260

Safety Update

See medical officer review page 7.

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-241 Supplement Type (e.g. SE5):

Supplement Number:

Stamp Date: June 25, 2002

Action Date: August 22, 2002

HFD-580

Trade and generic names/dosage form: ORTHO TRI-CYCLEN Lo (norgestimate/ethinyl estradiol)
Tablets

Applicant: Johnson & Johnson Pharmaceutical Research

Therapeutic Class: 3S

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Safety and efficacy of ORTHO TRI-CYCLEN Lo Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min kg mo. yr. Tanner Stage

Max kg mo. yr. Tanner Stage

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-960/ Terrie Crescenzi

(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301/594-7337**

**APPEARS THIS WAY
ON ORIGINAL**

NDA ##-###
Page 3

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Adult studies ready for approval
 Formulation needed
 Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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ON ORIGINAL**

NDA ##-###

Page 4

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-960/ Terrie Crescenzi

(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301/594-7337**

**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
8/22/02 12:57:19 PM
CSO

Daniel A. Shames
8/22/02 01:45:47 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Request for waiver of requirement to provide pediatric use information on _____ as per 21 CFR 314.55

_____ is indicated for the _____

The development of the ability to conceive is the defining event in human biology that separates adults from children. The development of the ability to conceive is associated with endocrinological maturity and the attainment of maximum height. From a strictly biologic point of view, anyone who is in need of a product to assist in the "prevention of pregnancy" is an adult. In spite of these biologic facts all subjects age 16 years or less are classified as "pediatric" for labeling purposes. This means that for certain individuals between the ages of 10 and 16 biologically mature "adults" will be classified as "pediatric".

_____ was studied in biologically mature women who desired contraception. The subjects with the lowest age in the study population were 18 years old. The safety and efficacy of _____ is expected to be the same for all biologically mature women whether 18 years or older, or 17 years and younger.

Therefore a full waiver of the pediatric requirements (21 CFR 314.55) is hereby requested. The basis for this request is that the product is for _____ and that the indication defines the correct population of biologically mature individuals who are eligible for its use. Those eligible for the prevention of pregnancy are separated from their immature counterparts not based on age but on biology. This product would be unsafe if prescribed to pediatric patients based only on age because below age 16 there are individuals who have not attained their maximum height and who could be harmed by a reduction in maximum height through prolonged exposure to an estrogen product.

The safety and efficacy of _____TM has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Abuse Liability
N/A

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ISI
8/21/02

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol

R.W. Johnson Research Pharmaceutical Institute

3S

PM: Jennifer Mercier
HFD-580
7-4260

Abuse Liability

N/A

JSM
01/19/01

APPEARS THIS WAY
ON ORIGINAL

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Microbiology Review
N/A

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8/21/02
O

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ON ORIGINAL

NDA 21-241

ORTHO TRI-CYLEN® Lo
norgestimate/ethinyl estradiol

3S

R.W. Johnson Research Pharmaceutical Institute

PM: Jennifer Mercier
HFD-580
7-4260

EA Review

See Chemistry Review #1, page 54.

Handwritten:
ISI
8/22/02

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NDA 21-241

ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol

R.W. Johnson Research Pharmaceutical Institute

3S

PM: Jennifer Mercier
HFD-580
7-4260

Microbiology Review

N/A

J. ISI
6/14/01

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

ORTHO TRI-CYCLEN® Lo
(norgestimate/ethinyl estradiol) Tablets

Johnson & Johnson Pharmaceutical Research Institute
3S

PM: Jennifer Mercier
HFD-580
7-4260

Statistical Reviews of Carcinogenicity studies

N/A

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8/22/02

NDA 21-241

**ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol**

R.W. Johnson Research Pharmaceutical Institute

3S

**PM: Jennifer Mercier
HFD-580
7-4260**

Statistical Reviews of Carcinogenicity Studies

N/A

*ISI
6/14/01*

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**APPEARS THIS WAY
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NDA 21-241

ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol

R.W. Johnson Research Pharmaceutical Institute

3S

PM: Jennifer Mercier
HFD-580
7-4260

Carcinogenicity Review

N/A

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ON ORIGINAL

NDA 21-241

**ORTHO TRI-CYCLEN™ Lo
norgestimate/ethinyl estradiol**

R.W. Johnson Research Pharmaceutical Institute

3S

**PM: Jennifer Mercier
HFD-580
7-4260**

CAC/ECAC Report

N/A

*JSI
6/14/01*

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-241

ORTHO TRI-CYCLEN® Lo
(norgestimate/ethinyl estradiol) Tablets

Johnson & Johnson Pharmaceutical Research Institute
3S

PM: Jennifer Mercier
HFD-580
7-4260

CAC/ECAC Report

N/A

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8/22/02

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