

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**19-653/S-031 & 19-697/S-028**

***Trade Name:*** Ortho-Cyclen 0.25mg/0.035mg  
Ortho Tri-Cyclen 0.18mg/0.035mg,  
0.215mg/0.035mg, 0.25mg/0.035mg

***Generic Name:*** norgestimate/ethinyl estradiol tablets

***Sponsor:*** Johnson RW

***Approval Date:*** 01/16/2002

***Indications:*** Ortho-Cyclen & Ortho Tri-Cyclen: For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Ortho Tri-Cyclen: For the treatment of moderate acne vulgaris in females, greater than or equal to 15 years of age, who have no known contradictions to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**19-653/S-031 & 19-697/S-028**

## CONTENTS

### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
<b>Approvable Letter</b>	
<b>Labeling</b>	
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**19-653/S-031 & 19-697/S-028**

**APPROVAL LETTER**



NDA 19-653/S-031

NDA 19-697/S-028

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

Dear Ms. Panasewicz:

Please refer to your supplemental new drug application dated July 25, 2001, received July 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO-CYCLEN® (norgestimate/ethinyl estradiol) Tablets and ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the option to use  as an alternative to the  for the  of the drug product tablets at the Raritan, New Jersey facility.

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

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

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

Sincerely,

*{See appended electronic signature page}*

David Lin, 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

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

/s/

-----  
David T. Lin  
1/16/02 12:52:37 PM  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-031 & 19-697/S-028**

**CHEMISTRY REVIEW(S)**

**CHEMIST REVIEW  
OF SUPPLEMENT**

- 1. ORGANIZATION:** DRUDP HFD-580
- 2. NDA NUMBER:** 19-653/SCM-031
- 3. SUPPLEMENT NUMBERS/DATES:**  
Letterdate: 25-JUL-2001  
Stampdate: 26-JUL-2001
- 4. AMENDMENTS/REPORTS/DATES:**  
Letterdate:  
Stampdate:
- 5. RECEIVED BY CHEMIST:** 30-JUL-2001

**6. APPLICANT NAME AND ADDRESS:**

R.W. Johnson Pharmaceutical Research Institute  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869-0602

**7. NAME OF DRUG:**

Ortho-Cyclen Tablets

**8. NONPROPRIETARY NAME:**

Norgestimate/ethinyl estradiol (NGM/EE)

**9. CHEMICAL NAME/STRUCTURE:**

- a. Norgestimate: a) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime acetate  
b) 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17 $\alpha$ )-(+)
- b. Ethinyl estradiol: a) 19-Nor-17 $\alpha$ -pregn-1,3,5(10)-trien-20-yne-3,17-diol  
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )

see UPS Dictionary of Drug Names for structures.

**10. DOSAGE FORM(S):**

Tablet

**11. POTENCY:**

250  $\mu$ g/35  $\mu$ g Norgestimate/ethinyl estradiol

**12. PHARMACOLOGICAL CATEGORY:**

Progestin, estrogen/Contraception

**13. HOW DISPENSED:**

RX

**14. RECORDS & REPORTS CURRENT:**

Yes

**15. RELATED IND/NDA/DMF:**  
NDA 19-697/SCM-028

**16. SUPPLEMENT PROVIDES FOR:**

The option to use [redacted] as an alternative to the [redacted] for the [redacted] of the drug product tablets at the Raritan, New Jersey facility.

**17. COMMENTS**

This Supplement-Changes Being Effected in 30 days provides for an option to use [redacted] as an alternative to the [redacted] for the [redacted] of Ortho-Cyclen and Ortho Tri-Cyclen tablets at the Raritan, NJ facility. A picture of the [redacted] has been included in the submission, but could not be reproduced clearly to be attached electronically to this review.

The sponsor has presented data for the 250 µg norgestimate/35 µg ethinyl estradiol strength tablets to demonstrate that the [redacted] process utilizing the [redacted] is consistent in all measurable parameters as product utilizing the current [redacted]. This strength tablet represents the monophasic product, Ortho-Cyclen, and the high dose strength tablet in the triphasic product, Ortho Tri-Cyclen. The [redacted] will also be used for the [redacted] of the other two strength tablets in Ortho Tri-Cyclen, the 180 µg norgestimate/35 µg ethinyl estradiol and 215 µg norgestimate/35 µg ethinyl estradiol tablets. A review of the data presented follows in the Review Notes section.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

This CBE-30 Supplement may be approved. **Issue an approval letter.**

**19. REVIEWER NAME**

David T. Lin, Ph.D.  
Chemistry Team Leader

**SIGNATURE**

**DATE COMPLETED**

14-JAN-2002

cc: Original: NDA 19-653/SCM-031

HFD-580/Division File  
HFD-580/JMercier  
HFD-580/DLin

INIT by

Filename: S19653.031 (doc)



1 Page(s) Withheld

Chemistry Review (19-653/S-031)

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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

/s/

-----  
David T. Lin  
1/14/02 05:15:07 PM  
CHEMIST  
I concur.

CHEMIST REVIEW  
OF SUPPLEMENT

1. ORGANIZATION: DRUDP HFD-580
2. NDA NUMBER: 19-697/SCM-028
3. SUPPLEMENT NUMBERS/DATES:  
Letterdate: 25-JUL-2001  
Stampdate: 26-JUL-2001
4. AMENDMENTS/REPORTS/DATES:  
Letterdate:  
Stampdate:
5. RECEIVED BY CHEMIST: 30-JUL-2001

6. APPLICANT NAME AND ADDRESS:

R.W. Johnson Pharmaceutical Research Institute  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869-0602

7. NAME OF DRUG:

Ortho Tri-Cyclen Tablets

8. NONPROPRIETARY NAME:

Norgestimate/ethinyl estradiol (NGM/EE)

9. CHEMICAL NAME/STRUCTURE:

- a. Norgestimate: a) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime acetate  
b) 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17 $\alpha$ )-(+)
- b. Ethinyl estradiol: a) 19-Nor-17 $\alpha$ -pregn-1,3,5(10)-trien-20-yne-3,17-diol  
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )

see UPS Dictionary of Drug Names for structures.

10. DOSAGE FORM(S):

Tablet

11. POTENCY:

180  $\mu$ g /35  $\mu$ g, 215  $\mu$ g /35  $\mu$ g, and 250  $\mu$ g /35  $\mu$ g Norgestimate/ethinyl estradiol

12. PHARMACOLOGICAL CATEGORY:

Progestin, estrogen/Contraception

13. HOW DISPENSED:

RX

14. RECORDS & REPORTS CURRENT:

Yes

**15. RELATED IND/NDA/DMF:**

NDA 19-653/SCM-031

**16. SUPPLEMENT PROVIDES FOR:**

The option to use [ ] as an alternative to the [ ] for the [ ] of the drug product tablets at the Raritan, New Jersey facility.

**17. COMMENTS**

This Supplement-Changes Being Effected in 30 days provides for an option to use [ ] as an alternative to the [ ] for the [ ] of Ortho-Cyclen and Ortho Tri-Cyclen tablets at the Raritan, NJ facility. A picture of the [ ] has been included in the submission, but could not be reproduced clearly to be attached electronically to this review.

The sponsor has presented data for the 250 µg norgestimate/35 µg ethinyl estradiol strength tablets to demonstrate that the [ ] process utilizing the [ ] is consistent in all measurable parameters as product utilizing the current [ ]. This strength tablet represents the monophasic product, Ortho-Cyclen, and the high dose strength tablet in the triphasic product, Ortho Tri-Cyclen. The [ ] will also be used for the [ ] of the other two strength tablets in Ortho Tri-Cyclen, the 180 µg norgestimate/35 µg ethinyl estradiol and 215 µg norgestimate/35 µg ethinyl estradiol tablets. A review of the data presented follows in the Review Notes section.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

This CBE-30 Supplement may be approved. **Issue an approval letter.**

**19. REVIEWER NAME**

David T. Lin, Ph.D.  
Chemistry Team Leader

**SIGNATURE**

**DATE COMPLETED**

14-JAN-2002

cc: **Original: NDA 19-697/SCM-028**

**HFD-580/Division File**

**HFD-580/JMercier**

**HFD-580/DLin**

**INIT by**

Filename: S19697.028 (doc)

1 Page(s) Withheld

Chemistry Review (19-697/S-028)

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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

/s/

-----  
David T. Lin  
1/14/02 05:19:06 PM  
CHEMIST  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-031 & 19-697/S-028**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 19-653

**CBE-30 SUPPLEMENT**

The R.W. Johnson Pharmaceutical Research Institute  
Attention: Donna Panasewicz  
Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

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

Name of Drug Product: Ortho-Cyclen® (norgestimate/ethinyl estradiol) Tablets  
NDA Number: 19-653  
Supplement number: S-031  
Date of supplement: July 25, 2001  
Date of receipt: July 26, 2001

This supplemental application was submitted as a "Supplement - Changes Being Effected in 30 days." The appropriateness of reporting the proposed change as changes being effected in 30 days is under review.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 24, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

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



NDA-19-653/S-031

Page 2

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

Sincerely,

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

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

/s/

-----  
Terri F. Rumble  
7/30/01 03:53:17 PM



NDA 19-697

**CBE-30 SUPPLEMENT**

The R.W. Johnson Pharmaceutical Research Institute  
Attention: Donna Panasewicz  
Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

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

Name of Drug Product:	Ortho Tri-Cyclen® (norgestimate/ethinyl estradiol) Tablets
NDA Number:	19-697
Supplement number:	S-028
Date of supplement:	July 25, 2001
Date of receipt:	July 26, 2001

This supplemental application was submitted as a "Supplement - Changes Being Effected in 30 days." The appropriateness of reporting the proposed change as changes being effected in 30 days is under review.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 24, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

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

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

Sincerely,

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

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

/s/

-----  
Terri F. Rumble  
7/30/01 04:13:46 PM



ORIGINAL



THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

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

NDA NO. 19-697 REF. NO. SCM-028 25 JUL 2001  
NDA SUPPL FOR Manufacturing

Susan Allen, MD MPH, Director  
US Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug  
Products, HFD-580  
Attn.: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20852

NDA 19-653  
ORTHO-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

NDA 19-697  
ORTHO TRI-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

SUPPLEMENT - CHANGES  
BEING EFFECTED IN 30  
DAYS

Dear Dr. Allen:

Reference is made to our approved New Drug Application(s) 19-653 and 19-697 for ORTHO-CYCLEN Tablets (norgestimate/ethinyl estradiol) and ORTHO TRI-CYCLEN Tablets, respectively. At this time, we are submitting a Changes Being Effected in 30 days Supplement to provide for the option to use  as an alternative to the  currently used for the  of ORTHO-CYCLEN and ORTHO TRI-CYCLEN Tablets at our Raritan, New Jersey facility.

In support of this change, we have appended comparative hardness, weight, thickness, and dissolution data for our 250 µg norgestimate/35 µg ethinyl estradiol containing tablets, which represents our monophasic product, ORTHO-CYCLEN Tablets, and the high dose strength in our triphasic product, ORTHO TRI-CYCLEN Tablets. The alternate  will also be utilized in the  process for the other two components of ORTHO TRI-CYCLEN Tablets, the 180 µg norgestimate/35 µg ethinyl estradiol and 215 µg norgestimate/35 µg ethinyl estradiol strength tablets. These tablets are manufactured using the same procedures and  parameters as the 250 µg norgestimate/35 µg ethinyl estradiol strength tablets.

The appended data demonstrates that the  process utilizing the   is consistent in all measurable parameters as product produced utilizing the current  and that there is no change in the safety, quality or efficacy of the products.

*Handwritten signature and date: L.H. Miller 7/16/01*

NACYCLEN-TRICYCLEN-CBE-30  DOC/16 JULY, 2001/J&J

A field copy of this submission is being forwarded directly to the FDA district office in North Brunswick, New Jersey. We certify that the field copy is a true copy of the information contained in the archival and review copies of this supplemental application.

Should you have any questions and/or comments, please contact me directly at (908) 218-6140 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson  
Pharmaceutical Research Institute



Donna Panasewicz  
Director  
Regulatory Affairs

Enclosure(s)