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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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/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-17α-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, (17α)-(+)

   b. Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
      b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)

   see UPS Dictionary of Drug Names for structures.

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

11. **POTENCY:**
    250 µg/35 µg 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 [ ]; 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 **SIGNATURE** **DATE COMPLETED**
David T. Lin, Ph.D. 14-JAN-2002
Chemistry Team Leader

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

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/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-17α-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, (17α)-(+)

   b. Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
      b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)

   see UPS Dictionary of Drug Names for structures.

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

11. **POTENCY:**
    180 µg /35 µg, 215 µg /35 µg, and 250 µg /35 µg 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	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Chemistry Team Leader		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

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/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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

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/s/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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/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.

N:\CYCLEN-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)