CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-653/S-030 & 19-697/S-027

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: 07/09/2001

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-030 & 19-697/S-027

CONTENTS

Reviews / Information Included in this NDA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-030 & 19-697/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-488/S-107
NDA 17-489/S-090
NDA 17-735/S-091
NDA 17-919/S-073
NDA 18-354/S-041
NDA 18-985/S-037
NDA 19-004/S-026
NDA 19-653/S-030
NDA 19-697/S-027

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 applications dated March 8, 2001, received March 9, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug products:

MODICON 21 (norethindrone/ethinyl estradiol) Tablets
ORTHO-NOVUM 1/35 21 (norethindrone/ethinyl estradiol) Tablets
MODICON 28 (norethindrone/ethinyl estradiol) Tablets
ORTHO-NOVUM 1/35 28 (norehtindrone/ethinyl estradiol) Tablets
ORTHO-NOVUM 10/11 21 & 28 (norehtindrone/ethinyl estradiol) Tablets
ORTHO-NOVUM 7/7/7 21 & 28 (norethindrone/ethinyl estradiol) Tablets
ORTHO-NOVUM 7/14 (norethindrone/ethinyl estradiol) Tablets
ORTHO-CYCLEN ([ ]ethinyl estradiol) Tablets
ORTHO TRI-CYCLEN ([ ]ethinyl estradiol) Tablets.

We acknowledge receipt of your submissions dated March 16, 2001.

These "Changes Being Effected in 30 days" supplemental new drug applications provide for the option to use [ ] ethinyl estradiol drug substance as an alternative to the [ ] material currently used in the manufacture of the drug product.

We have completed the review of these supplemental applications, and they are 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}

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

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

/s/

Moo-Jhong Rhee
7/9/01 04:22:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-030 & 19-697/S-027

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 19-653/SCS-030
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 08-MAR-2001
   Stampdate: 09-MAR-2001
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate:
   Stampdate:
5. **RECEIVED BY CHEMIST:** 23-MAR-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 17-488/SCS-107, NDA 17-489/SCS-090, NDA 17-735/SCS-091, NDA 17-919/SCS-073, NDA 18-354/SCS-041, NDA 18-985/SCS-037, NDA 19-004/SCS-026, NDA 19-697/SCS-027

16. SUPPLEMENT PROVIDES FOR:
The option to use [ ] ethinyl estradiol (EE) drug substance as an alternative to the [ ] [ ] material currently used in the manufacture of the drug product.

17. COMMENTS
This Supplement-Changes Being Effected in 30 days provides for an option to use [ ] ethinyl estradiol (EE) drug substance as an alternative to the [ ] material currently used in the manufacture of the drug product. It has been stated that without the option to use [ ] [ ] EE, the sponsor is facing with the inability to continue to manufacture drug product for an interim period of time due to capacity issues of one of the suppliers of EE, [ ].
The amendment (03/16/01) was submitted in response to a t-con between Donna Panasewicz of the R. W Johnson and Terry Rumble and Jennifer Mercier of the Agency, to make the submission clear by submitting two separate amendments: one for norethindrone/ethinyl estradiol drug products and one for norgestimate/ethinyl estradiol drug products.
The sponsor justified that the drug products would not have any impact due to use of [ ] EE because: a) drug product is manufactured by [ ] process; b) the process involved [ ] The justification is deemed satisfactory.
The sponsor has committed to place the first batch of each product using the [ ] material on marketed stability with the results reported in the annual reports.

18. CONCLUSIONS AND RECOMMENDATIONS:
This CBE Supplement may be approved. **Issue an approval letter.**

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		02-JUL-2001

cc: Original: NDA 19-653/SCS-030
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S19653.030 (doc)

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
7/3/01 03:00:39 PM
CHEMIST
Bundled supplement for use of [ ] EE.

Moo-Jhong Rhee
7/3/01 06:29:27 PM
CHEMIST
I concur

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 19-697/SCS-027
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 08-MAR-2001
   Stampdate: 09-MAR-2001
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate:
   Stampdate:
5. **RECEIVED BY CHEMIST:** 23-MAR-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 17-488/SCS-107, NDA 17-489/SCS-090, NDA 17-735/SCS-091, NDA 17-919/SCS-073, NDA 18-354/SCS-041, NDA 18-985/SCS-037, NDA 19-004/SCS-026, NDA 19-653/SCS-030

16. SUPPLEMENT PROVIDES FOR:
The option to use [ ] ethinyl estradiol (EE) drug substance as an alternative to the [ ] [ ] material currently used in the manufacture of the drug product.

17. COMMENTS
This Supplement-Changes Being Effected in 30 days provides for an option to use [ ] ethinyl estradiol (EE) drug substance as an alternative to the [ ] material currently used in the manufacture of the drug product. It has been stated that without the option to use [ ] [ ] EE, the sponsor is facing with the inability to continue to manufacture drug product for an interim period of time due to capacity issues of one of the suppliers of EE, [ ]
The amendment (03/16/01) was submitted in response to a t-con between Donna Panasewicz of the R. W Johnson and Terry Rumble and Jennifer Mercier of the Agency, to make the submission clear by submitting two separate amendments: one for norethindrone/ethinyl estradiol drug products and one for norgestimate/ethinyl estradiol drug products.
The sponsor justified that the drug products would not have any impact due to use of [ ] EE because: a) drug product is manufactured by [ ] process; b) the process involved [ ] The justification is deemed satisfactory.
The sponsor has committed to place the first batch of each product using the [ ] material on marketed stability with the results reported in the annual reports.

18. CONCLUSIONS AND RECOMMENDATIONS:
This CBE Supplement may be approved. **Issue an approval letter.**

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		02-JUL-2001

cc: Original: NDA 19-697/SCS-027
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S19697.027 (doc)

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
7/3/01 02:57:47 PM
CHEMIST
Bundled supplement for use of [ ] EE.

Moo-Jhong Rhee
7/3/01 05:12:35 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-030 & 19-697/S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-653/S-030
NDA 19-697/S-027

CBE-30 SUPPLEMENT

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 applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
19-653	S-030	ORTHO-CYCLEN® (norgestimate/ehtinyl estradiol) Tablets
19-697	S-027	ORTHO TRI-CYCLEN® norgestimate/ethinyl estradiol) Tablets

Date of Supplements: March 8, 2001

Date of Receipt: March 9, 2001

We also acknowledge receipt of your submission dated March 16, 2001, amending these supplements.

These supplemental applications, submitted as "Supplement - Changes Being Effected in 30 days" supplements propose for the use of both [ ] and [ ] ethinyl estradiol (EE) drug substance from [ ] the currently approved supplier of [ ] material currently used in the manufacture of these products produced by the [ ] process.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on May 8, 2001 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be September 9, 2001.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

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

If you have any questions, 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
Center for Drug Evaluation and Research

/s/

Terri F. Rumble
3/19/01 06:16:23 PM

ORIGINAL

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

NDA SUPP AMEND
SCS-027-BL

16 MAR 2001

Susan Allen, MD, MPH, 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 19-653
ORTHO-CYCLEN®
(norgestimate/ethinyl estradiol) Tablets
NDA 19-697
ORTHO TRI-CYCLEN®
(norgestimate/ethinyl estradiol) Tablets

AMENDMENT TO SUPPLEMENT – Changes Being Effected In 30 Days Dated 8 March 2001

See Chem-Rev. DTC 7/13/01

Dear Dr. Allen:

Reference is made to the above approved New Drug Applications for our norgestimate/ethinyl estradiol containing oral contraceptive products and to our Changes Being Effected in 30-Days Supplement dated 8 March 2001. Reference is further made to subsequent telephone conversations between Donna Panasewicz of the R. W. Johnson Pharmaceutical Research Institute and Terry Rumble and Jennifer Mercier of your Division in which we were asked to amend the supplement for clarity. It was agreed that we would submit two separate amendments: one for our norethindrone/ethinyl estradiol containing oral contraceptive products and one for our norgestimate/ethinyl estradiol containing oral contraceptive products

As requested at this time we are amending our 8 March 2001 Special Supplement - Changes Being Effected in 30 Days to provide for the use of both [ ] and [ ] ethinyl estradiol (EE) drug substance from [ ] our currently approved supplier of [ ] EE for our norgestimate/ethinyl estradiol containing oral contraceptives produced by the [ ] process. This request is necessitated due to capacity issues of the supplier. and without the option to use either [ ] EE we are faced with the inability to continue to manufacture drug product for an interim period of time. Because this is a [ ] [ ] the use of the [ ] material would not have an impact on the product itself.

We commit to place the first batch of each product using the [ ] material on marketed stability with the results reported in the annual reports.

REVIEWS COMPLETED
CSO ACTION: [X] LETTER [ ] N.A.L. [ ] MEMO
CSO INITIALS ZURICH 6/21 DATE

A field copy of this submission is being forwarded directly to the FDA district offices in North Brunswick, New Jersey and San Juan, Puerto Rico. 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 require any additional information, please contact me 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 M. Panasewicz
Director
Regulatory Affairs

ORIGINAL

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

08 MAR 2001

Susan Allen, MD, MPH, 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-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA NO. 19697 REF. NO. 027
NDA SUPPL FOR Control

See Chem Rev. DTL 3/3/01

REVIEWS COMPLETED

CSO ACTION:
[X] LETTER [ ] N.A.I. [ ] MEMO

CSO INITIALS DATE

NDA 17-488
MODICON® 21
(norethindrone/ethinyl estradiol) Tablets

Please cross refer to:

NDA 17-489
ORTHO NOVUM® 1/35 21
(norethindrone/ethinyl estradiol) Tablets

NDA 17-735
MODICON® 28
(norethindrone/ethinyl estradiol) Tablets

NDA 17-919
ORTHO-NOVUM® 1/35 28
(norethindrone/ethinyl estradiol) Tablets

NDA 18-354
ORTHO-NOVUM® 10/11
(norethindrone/ethinyl estradiol) Tablets

NDA 18-985
ORTHO-NOVUM® 7/7/7 21 & 28
(norethindrone/ethinyl estradiol) Tablets

NDA 19-004
ORTHO-NOVUM® 7/14
(norethindrone/ethinyl estradiol) Tablets

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

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

SUPPLEMENT – CHANGES BEING EFFECTED in 30 DAYS

Dear Dr. Allen:

Reference is made to the above approved New Drug Applications for our oral contraceptive products. At this time we are submitting a Special Supplement - Changes Being Effected in 30 Days to provide for the option to use [ ] ethinyl estradiol (EE) drug substance as an alternative to the [ ] material currently used in

the manufacture of these products produced by the [redacted] process. This request is necessitated due to capacity issues of one of our approved suppliers of drug substance, [redacted] and without the option to use either [redacted] EE we are faced with the inability to continue to manufacture drug product for an interim period of time. Because this is a [redacted], the use of the [redacted] material would not have an impact on the product itself.

We commit to place the first batch of each product using the [redacted] material on marketed stability with the results reported in the annual reports.

A field copy of this submission is being forwarded directly to the FDA district offices in North Brunswick, New Jersey and San Juan, Puerto Rico. 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 require any additional information, please contact me 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 M. Panasewicz
Director
Regulatory Affairs