

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**19-653/S-016 & 19-697/S-011**

***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:*** 08/02/1996

***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.

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*APPLICATION NUMBER:*  
**19-653/S-016 & 19-697/S-011**

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*APPLICATION NUMBER:*  
**19-653/S-016 & 19-697/S-011**

**APPROVAL LETTER**

ORIGINAL

NDA 19-653/S-016  
NDA 19-697/S-011

AUG 2 1996

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

Dear Ms. Panasewicz:

Please refer to your April 1, 1996, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

Ortho-Cyclen (norgestimate and ethinyl estradiol) Tablets, NDA 19-653; and  
Ortho-TriCyclen (norgestimate and ethinyl estradiol) Tablets, NDA 19-697.

These supplemental applications provide for a final dissolution specification, Q= 80% at 20 min (0.025% Tween), for both drug substances.

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, please contact Ms. Christina Kish at 310-827-4271.

Sincerely,

*Helen W. Davies* 8/02/96

Helen W. Davies, Ph.D.  
Chemistry Team Leader  
Division of New Drug Chemistry II  
Office of New Drug Chemistry, OPS  
@ Division of Reproductive and Urologic  
Drug Products (HFD-580)  
Center for Drug Evaluation and Research

NDA 19-653/S-016  
NDA 19-697/S-011

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cc:

Orig. NDA's (2)

HFD-580(2)

DISTRICT OFFICE

HFD-80

HFD-580/HDavies/MRhee

HFD-580/CKish/7.5.96/n19653ap.s16

concurrences:LPauls 7.31.96/MRhee 7.31.96/HDavies 7.31.96

SUPPLEMENT APPROVAL (S/AP)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-016 & 19-697/S-011**

**CHEMISTRY REVIEW(S)**

CHEMIST'S REVIEW

1. Organization  
DMEDP HFD-510

2. NDA Number  
19-653 JUL - 2 199

3. Name and Address of Applicant

The R.W. Johnson  
Pharmaceutical Research Institute  
Route 202, P.O. Box 300  
Raritan, NJ 08869-0602  
908-704-4038

4. Supplement

S-016  
7-2-96

ORIGINAL

5. Name of Drug

Ortho-Cyclen

6. Nonproprietary Name

Norgestimate/EE tablets

7. Supplement Provides For

A final dissolution specification, Q=80% at 20 min (0.025% Tween), for both drug substances.

8. Amendment

9. Pharmacological Category

Oral contraceptive

10. How Dispensed

RX

11. Related

NDA 19-697 (S-011)

12. Dosage form

Tablets for oral administration

13. Potency

250µg/35µg (norgestimate/EE)

14. Chemical Name and Structure

Norgestimate: 18,19-dinor-17-pregn-4-en-20-yn-3-on, 17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-

Empirical Formula: C<sub>23</sub>H<sub>31</sub>NO<sub>3</sub>

MW: 369.50

Ethinyl Estradiol: 19-nor-17-α-pregna-1,3,5-(10)-trien-20-yne-3,17-diol

Empirical Formula: C<sub>22</sub>H<sub>30</sub>O

MW: 296.41

15. Comments

This special supplement was submitted to notify the Agency of the final specification of the dissolution test, Q=80% 20 min for both drug substances. The Biopharm review supports the use of this specification. See Biopharm's review for detail.

16. Conclusion and Recommendation

This supplement is approvable. Issue an approval letter.

17. Name

Moo-Jhong Rhee, Ph.D.

Reviewer's Signature

Date

7-2-96

Distribution

R/D initialed by

SL.253

Original Jacket

H. Davis  
7/2/96

Reviewer/CSO

Division File

CHEMIST'S REVIEW

1. Organization  
DMEDP HFD-510

2. NDA Number  
19-697

3. Name and Address of Applicant

The R.W. Johnson  
Pharmaceutical Research Institute  
Route 202, P.O. Box 300  
Raritan, NJ 08869-0602  
908-704-4038

4. Supplement

S-011  
4-1-96

5. Name of Drug

Ortho Tri-Cyclen

6. Nonproprietary Name

Norgestimate/EE tablets

7. Supplement Provides For

A final dissolution specification, Q=80% at 20 min (0.025% Tween), for both drug substances.

8. Amendment

9. Pharmacological Category

Oral contraceptive

10. How Dispensed

RX

11. Related

NDA 19-653 (S-016)

12. Dosage form

Tablets for oral administration

13. Potency

180µg/35µg, 215µg/35µg, 250µg/35µg  
(norgestimate/EE)

14. Chemical Name and Structure

Norgestimate: 18,19-dinor-17-pregn-4-en-20-yn-3-on, 17-(acetyloxy)-13-ethyl-, oxime,(17α)-(+)-

Empirical Formula:  $C_{23}H_{31}NO_3$  MW: 369.50

Ethinyl Estradiol: 19-nor-17-α-pregna-1,3,5-(10)-trien-20-yne-3,17-diol

Empirical Formula:  $C_{22}H_{30}O$  MW: 296.41

15. Comments

This special supplement was submitted to notify the Agency of the final specification of the dissolution test, Q=80% 20 min for both drug substances. The Biopharm review supports the use of this specification. See Biopharm's review for detail.

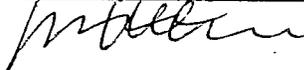
16. Conclusion and Recommendation

This supplement is approvable. Issue an approval letter.

17. Name

Moo-Jhong Rhee, Ph.D.

Reviewer's Signature



Date

7-2-96

Distribution

R/D initialed by

SL.252

Original Jacket

H. Davies  
7/2/96

Reviewer/CSO

Division File

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-016 & 19-697/S-011**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Date APR 30 1996

NDA No. 19-697

The R.W. Johnson Pharmaceutical Research Inst.  
Division of Ortho Pharmaceutical Corporation  
920 Route 202 South  
P.O. Box 300  
Raritan, New Jersey 08869-0602

Attention: Donna Panasewicz, Manager, Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ORTHO TRI-CYCLEN (Norgestimate + Ethinyl Estradiol)

NDA Number: 19-697

Supplement Number: 5-011S-011

Date of Supplement: April 1, 1996

Date of Receipt: April 16, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the

Act on JUN 15 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products  
Attention: Document Control Room  
5600 Fishers Lane, HFD-510  
Rockville, MD 20857

Sincerely yours,

  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office Drug Evaluation II  
Center for Drug Evaluation and Research

NDA NO. 19697 REV. NO. 014  
NDA SUPPLEMENT FOR SCF

ORIGINAL  
NDA SUPPLEMENT

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

APR 01 1996

Solomon Sobel, M.D.  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Review II, HFD #510  
ATTN: Document Control Room #14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

Special Supplement - Changes Being Effectuated

NDA 19-653  
ORTHO CYCLEN® (Norgestimate/Ethinyl  
Estradiol) Tablets.

NDA 19-697  
ORTHO TRI-CYCLEN® (Norgestimate/Ethinyl  
Estradiol) Tablets



Dear Dr. Sobel,

Reference is made to our supplemental new drug applications for ORTHO-CYCLEN, NDA 19-653 (S-009) and ORTHO TRI-CYCLEN, NDA 19-697 (S-002) submitted July 26, 1993 which provided for a new non-alcoholic based dissolution method, (DM91-020). Further reference is made to your approval letter dated February 16, 1995 in which it was requested that we establish a final dissolution specification after additional data are accrued for one year using dissolution method DM91-020.

At this time we are submitting our final dissolution specifications for norgestimate and ethinyl estradiol applicable to both product release and stability testing. The specifications are as follows:

- Norgestimate: Q=80% at 20 minutes
- Ethinyl Estradiol: Q=80% at 20 minutes.

*CSO: please let this be reviewed by Biopharm  
MJA 5/1/96*

As discussed at a meeting held with the agency on September 14, 1995 regarding Dissolution Method DM 91-020 we continue to experience variability in our dissolution results and our investigation into the reason for the variability as well as the increase in S2 testing since employing this method is on-going. Upon completion of our investigation we plan to discuss our findings and future steps with the agency.

Should you have any questions, you may contact me at (908) 704-4600 a number designated for FDA use only or if you prefer you may contact me directly at (908) 218-6140.

Very truly yours,  
The R.W. Johnson Pharmaceutical  
Research Institute

*Donna M. Panasewicz*  
Donna M. Panasewicz  
Manager  
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

LETTER  N.A.I.  MEMO

CSO INITIALS \_\_\_\_\_ DATE \_\_\_\_\_



*Notes  
K. Spang  
5/2/96*

cc: John Hunt