

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**19-697/S-009**

***Trade Name:*** 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:*** 02/07/1996

***Indications:*** For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception; and 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:*

**19-697/S-009**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-697/S-009**

**APPROVAL LETTER**

NDA 19-697/S-009

FEB - 7 1996

R.W. Johnson Pharmaceutical Research Institute  
Attention: Ms. Isabel B. Drzewiecki  
Senior Director, Regulatory Affairs  
Route 202, P.O.Box 300  
Raritan, N.J. 08869-0602

Dear Ms. Drzewiecki:

Please refer to your September 26, 1995, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO TRI-CYCLEN (norgestimate and ethinyl estradiol) Tablets.

We also refer to your amendment dated December 22, 1995, and February 1, 1996.

This supplemental application provides for the restoration of the expiration date from 24 months to the original 36 months with a relaxed specification of degradation product from % to 1%.

We have completed the review of this supplemental application and it is approved. However, we request that you implement a specification for the ratio of syn/anti isomers of norgestimate in the drug product using the HPLC method with a detection wavelength at 230 nm. This specification should be comparable to that of the drug substance determined at 254 nm.

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 310-443-3520.

Sincerely,



Helen W. Davies, Ph.D.  
Acting Supervisory Chemist I  
Division of New Drug Chemistry II  
Office of New Drug Chemistry, OPS  
@ Division of Metabolism and  
Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research



NDA 19-697/S-009

Page 2

cc:

Orig. NDA

HFD-510

DISTRICT OFFICE

HFD-80

HFD-510/HDavies/MRhee

HFD-510/CKish/2.2.96/n19697ap.s9

concurrences:MRhee 2.2.96/HDavies 2.2.96/LPauls for EGalliers 2.6.96

SUPPLIMENT APPROVAL (S/AP)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-697/S-009**

**CHEMISTRY REVIEW(S)**

**CHEMIST'S REVIEW**

**1. Organization**  
DMEDP HFD-510

**2. NDA Number** FEB - 2 1996  
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-009  
9-26-95

**5. Name of Drug**

Ortho Tri-Cyclen

**6. Nonproprietary Name**

Norgestimate/EE tablets

**7. Supplement Provides For**

Restoration of expiration date from 24-month to the original 36-month with relaxed specification of degradation product from /% to [ ]%

**8. Amendment**

12-22-95  
2-1-96

**9. Pharmacological Category**

Oral contraceptive

**10. How Dispensed**

RX

**11. Related**

NDA 19-697 (S-006)

**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<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: [ ]

MW: 296.41

**15. Comments**

This supplement was submitted to extend the expiration date from 24-month to 36-month with relaxation of the specification for the degradation product [ ] from /% to [ ]%. Other specifications, including the assay limits are unchanged. Originally, this product was approved with the expiration date of 36-month. However, on May 16, 1995, the firm submitted a supplement with "Changes Being Effected" for reducing the expiration date to 24-month because the stability batches did not meet the specification (/%) for the degradation product. A meeting was held with the firm on September 14, 1995 and at that meeting it was agreed to let the firm relax the specification for the degradation product to [ ]% provided that: 1) the firm confirm that [ ] is the only degradation product and, 2) its toxicity issue can be cleared by our pharmacologist. (cont'd)

**16. Conclusion and Recommendation**

This supplement is approvable. Issue an approval letter (see draft letter).

**17. Name**

Moo-Jhong Rhee, Ph.D.

**Reviewer's Signature**

**Date**

2-2-96

**Distribution**

**Original Jacket**

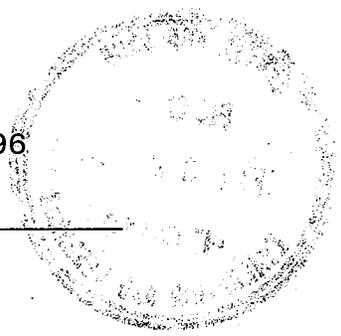
**Reviewer/CSO**

**Division File**

R/D initialed by

SL.238

H. Davis  
2/02/96



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of trade secret and/or

confidential commercial

information from

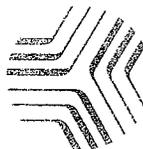
Chemistry Review: 19-697/S-009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-697/S-009**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

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

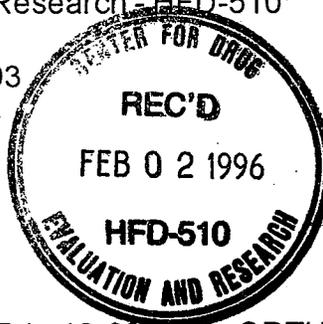
*See chem Rev #1 (of Supplement S-009)  
dated Feb. 2, 1996.  
MFR 2/5/96*

FEB 01 1996

Solomon Sobel, M.D. Director  
Division of Metabolism and Endocrine Drug Products  
Center for Drug Evaluation and Research - HFD-510  
Food and Drug Administration  
Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857

**Amendment to Supplement -  
Expedited Review Requested**

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



Dear Dr. Sobel:

Reference is made to our NDA 19-697 for ORTHO TRI-CYCLEN Tablets and specifically to our supplement dated September 26, 1995 in which we provided for the revision to our NDA requirement for total impurity testing for our mid and low-dose tablets. This revision reflected the following:

- that the only impurity detected is [ ]
- a revised stability specification for [ ] - less than or equal to [ ]%.
- a three year expiration date for ORTHO TRI-CYCLEN Tablets.

Further reference is made to the amendment to the above supplement dated December 22, 1995 in which we provided the HPLC chromatograms as requested by Dr. Moo Jong Rhee of your division.

We are providing at this time the peak area for the syn and anti peaks relevant to the chromatograms found in Appendix IX thru XIV of our December 22, 1995 supplement amendment as requested by Dr. Rhee during a telephone conversation on January 29, 1996. Additionally, we are also providing a corrected page for Appendix XI specific to the calculation for 12L502-1(B). In the original submission the total area norgestimate was given incorrectly as [ ]. The total area norgestimate is 1692101. This error has no impact on the final percent, which remains as 5.36%.

FEB 01 1996

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

Very truly yours,

The R.W. Johnson  
Pharmaceutical Research Institute



Donna Panasevicz  
Manager  
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

LETTER  
*DP*

N.A.I.  
*DP/1/96*

CSO INITIALS

DATE

Enclosures

DP:mp



ORIGINAL  
NDA SUPPL AMENDMENT  
325-009102

THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 200707, NEW JERSEY 08869-0602

DEC 22 1995



**Amendment to Supplement -  
Expedited Review Requested**

Solomon Sobel, M.D. Director  
Division of Metabolism & Endocrine Drug Products  
Center for Drug Evaluation and Research HFD-510  
Food and Drug Administration  
Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA 19-697**

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

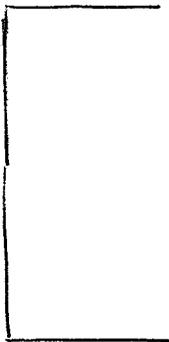
Dear Dr. Sobel:

Reference is made to our NDA 19-697 for ORTHO TRI-CYCLEN Tablets and specifically to our supplement dated September 26, 1995 in which we provided for the revision to our NDA requirement for total impurity testing for our mid and low-dose tablets. This revision reflected the following:

- that the only impurity detected is [ ]
- a revised stability specification for [ ] - less than or equal to [ ]%
- a return to a three year expiration date for ORTHO TRI-CYCLEN

Further reference is made to a telephone conversation on October 30, 1995 between Dr. Moo Jhong Rhee of the Agency and Mrs. Donna Panasewicz of The R.W. Johnson Pharmaceutical Research Institute during which Dr. Rhee requested that we supply the HPLC chromatograms and "hard data" to substantiate that the only impurity detected is [ ]. Dr. Rhee also requested that we provide for him a timeframe in which our internal investigation regarding the increase in [ ] will be completed and a written report supplied.

At this time, we wish to provide the items requested by Dr. Rhee .



We have included in Item I a summary of data by batch number, supplier, test station and % [ ] . The substantiating data including HPLC Chromatograms are included in Item II.

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

REVIEWS COMPLETED

CSO ACTION:	
<input checked="" type="checkbox"/> LEI	<input type="checkbox"/> N.A.I.
CSO 1111	DATE

*2/7/96*

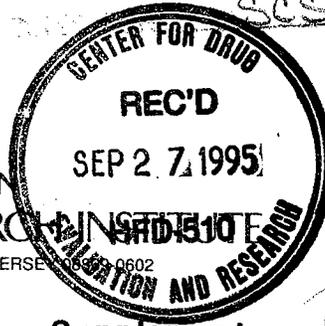
Very truly yours,

The R. W. Johnson  
Pharmaceutical Research Institute

Donna Panasewicz  
Manager  
Regulatory Affairs

19697 009

SCS ORIGINAL



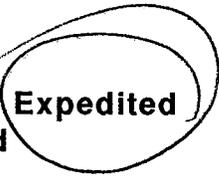
NEW SUPPLEMENT

THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE  
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08859-0602

SEP 26 1995

Solomon Sobel, M.D. Director  
Division of Metabolism and Endocrine Drug Products  
Center for Drug Evaluation and Research - HFD-510  
Food and Drug Administration  
Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857

Supplement -  
Review Requested



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

Dear Dr. Sobel:

Reference is made to our NDA 19-697 for ORTHO TRI-CYCLEN and specifically to a meeting held on September 14, 1995, between representatives of The R.W. Johnson Pharmaceutical Research Institute and representatives of the Agency, during one portion of which we discussed our current stability specification for total impurities pertinent to our ORTHO TRI-CYCLEN low and mid dose tablets. Further reference is made to a telephone conversation between Mrs. I. Drzewiecki, of The R.W. Johnson Pharmaceutical Research Institute, and Dr. A. Jordan, of your Division, on September 15, 1995, and a subsequent letter which was submitted to the Agency on September 19, 1995, confirming Mrs. Drzewiecki's agreement with Dr. Jordan that no additional toxicological data will be required to modify our current stability specification for total impurities (Attachment I).

Additionally, reference is made to our Special Supplement - Changes Being Effected submitted on May 16, 1995, for purposes of reducing the expiration dating of ORTHO TRI-CYCLEN Tablets from 36 months to 24 months. This action was taken due to the fact that the specification of /% for Total Impurities had been exceeded in two batches of ORTHO TRI-CYCLEN Tablets at 32 months. Included in that supplement was a copy of an NDA Field Alert dated May 5, 1995, which reported this fact and that it was the  that exceeded the /% upper limit.

At this time, we wish to submit a Supplement - Expedited Review Requested, to accomplish the following:

- Revise the NDA requirement for a Total Impurity testing to reflect that the only impurity detected is  as requested by the Agency at the September 14, 1995 meeting.
- Establish a revised stability specification for  which will be  $\leq$   %.
- Return to a three year expiration date for ORTHO TRI-CYCLEN.

An evaluation of the data from the three tablet strengths of ORTHO TRI-CYCLEN Tablets indicates that for lower strengths of norgestimate a higher percentage of [ ] is formed. For the NRG 0.250/EE 0.35 mg. tablets, the high dose of ORTHO TRI-CYCLEN and also marketed as the monophasic product ORTHO-CYCLEN, the [ ] levels remained well below 1% over 36 months. The total impurity stability specification for the NRG 0.250 mg/EE 0.35 mg. will remain at ≤1%. Additionally, the release specification for total impurities for all three dosage strengths will remain at ≤1%.

Based upon the results of our investigation and the fact that the original NDA specification of 1% was based upon limited data, at this time, we are proposing the changes described above. We believe that a slight increase in the level of [ ] has no impact on the safety and efficacy of this product for the reasons cited in the May 5, 1995, memorandum from Dr. J.S. Lippman, submitted with the supplement dated May 16, 1995, and included here as Attachment 3 for ease of review. This revised specification will support a shelf-life of 36 months. Accordingly, we also wish to return to an expiration dating of 36 months from date of manufacture as was originally approved for this product.

We certify that an identical copy of this supplement is being forwarded to FDA District Office on the date of this letter.

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

REVIEWS COMPLETED

Very truly yours,

CSO ACTION:

The R.W. Johnson  
Pharmaceutical Research Institute

LETTER

N.A.K.



CSO INITIALS

DATE

Donna Panasewicz  
Manager  
Regulatory Affairs

DP/lg  
Enclosures

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

Date OCT 13 1995

NDA No. 19-697

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

Attention: Donna Panasewicz

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ORTHO TRI-CYCLEN

NDA Number: 19-697

Supplement Number: S-009

Date of Supplement: September 26, 1995

Date of Receipt: September 27, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Attention: Document Control Room 14B-03  
5600 Fishers Lane, HFD-510  
Rockville, MD 20857

Sincerely yours,

Supervisory Consumer Safety Officer  
Division of Metabolism and Endocrine Drug Products  
Center for Drug Evaluation and Research