

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**19-653/S-021 & 19-697/S-016**

***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:*** 11/02/1999

***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-021 & 19-697/S-016**

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<b>Summary Review</b>	
<b>Officer/Employee List</b>	
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**19-653/S-021 & 19-697/S-016**

**APPROVAL LETTER**

NDA 19-653/S-021  
NDA 19-697/S-016

OCT - 2

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

NOV - 2 1999

Dear Ms. Panasewicz:

Please refer to your supplemental new drug applications dated November 10, 1998, received November 12, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ortho-Cyclen Tablets and Ortho Tri-Cyclen Tablets.

We acknowledge receipt of your submission dated July 1, 1999. Your submission of July 1, 1999 constituted a complete response to our May 12, 1999 action letter.

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

These supplemental new drug applications provide for changes in the packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle.

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, contact Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*Moo-Jhong Rhee* 10/29/99

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

NDA 19-653/S-021  
NDA 19-697/S-016  
Page 2

cc:

Archival NDAs 19-653, 19-697  
HFD-580/Div. Files  
HFD-580/J.Mercier  
HFD-580/Rhee/Lin  
HFD-095/DDMS-IMT  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

Drafted by: JM/October 25, 1999

Initialed by: Rumble10.27.99/Lin10.28.99/Rhee10.28.99/Lin10.29.99

final: October 29, 1999

filename: 19653S21.WPD

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**19-653/S-020 & 19-697/S-015**

**APPROVABLE LETTER**

NDA 19-697/S-016  
NDA 19-653/S-021

R. W. Johnson  
Attention: Donna M. Panasewicz  
Manager, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Rariton, NJ 08869-0602

MAY 12 1999

Dear Ms. Panasewicz:

Please refer to your supplemental new drug applications dated November 10, 1998, received November 12, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO-TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets and ORTHO-CYCLEN (norgestimate/ethinyl estradiol) Tablets, NDA 19-697 and NDA 19-653, respectively.

We acknowledge receipt of your submission dated December 2, 1998.

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

These supplements propose the following change: a change in packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle. Your submission stated December 12, 1998 as the implementation date for the changes.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

1. Provide the following long-term stability data of the drug product which has been packaged in the new blister pack:
  - a) 18-months on one batch at 25<sup>0</sup> C/60% RH, and
  - b) 12-months on two batches at 25<sup>0</sup> C/60% RH.
2. Provide the results of the leak testing on the new empty blister packs.
3. Commit to provide the following additional stability data:
  - a) 24-months on one batch at 25<sup>0</sup> C/60% RH, and
  - b) 18-months on two batches at 25<sup>0</sup> C/60% RH.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a

NDA 19-697/S-016

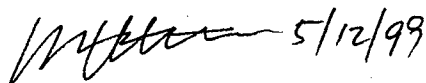
NDA 19-653/S-021

Page 2

partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, contact Jennifer Mercier, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

 5/12/99

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

cc:

Archival NDAs 19-697, 19-653  
HFD-580/Div. Files  
HFD-580/T.Rumble/Mercier  
HFD-580/Rarick/Mann/Rhee/Lin  
HFD-95/DDMS  
DISTRICT OFFICE

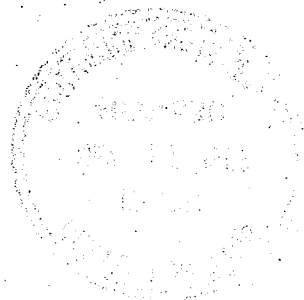
Drafted by: tfr/May 11, 1999

Initialed by: Rarick,5.12.99/Mann,5.11.99/Rhee,5.11.99/Lin,5.11.99

Final: Rumble.5.12.99

Filename: 19653.WPF

APPROVABLE (AE)





**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-021 & 19-697/S-016**

**CHEMISTRY REVIEW(S)**

MAY 10 1999

CHEMIST REVIEW  
OF SUPPLEMENT

1. ORGANIZATION: DRUDP HFD-580
2. NDA NUMBER: 19-697/SCM-016
3. SUPPLEMENT NUMBERS/DATES:  
Letterdate: 10-NOV-1998  
Stampdate: 12-NOV-1998
4. AMENDMENTS/REPORTS/DATES:  
Letterdate: 02-DEC-1998  
Stampdate: 03-DEC-1998
5. RECEIVED BY CHEMIST: 20-NOV-1998

## 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:

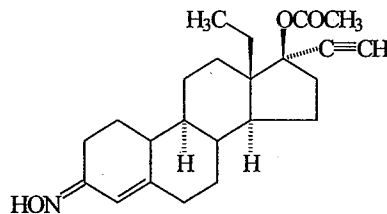
Ortho Tri-Cyclen Tablets

## 8. NONPROPRIETARY NAME:

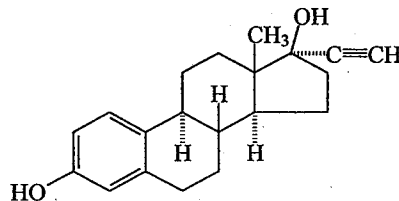
Norgestimate/ethinyl estradiol (NGM/EE)

## 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 $\alpha$ )



## 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

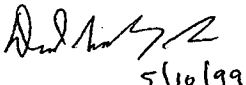
**15. RELATED IND/NDA/DMF:**  
NDA 19-653/SCM-021

**16. SUPPLEMENT PROVIDES FOR:**  
Change in packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle.

**17. COMMENTS**  
The company will be replacing the current Dialpak Tablet Dispenser with Dialpak III Tablet Dispenser. This involves the replacement of the current packaging equipment with new equipment. The new equipment are newer versions of the currently used equipment and the packaging operation will remain the same. In addition the same [ ] and aluminum foil will be used for the blister package. The blister packages from the two dialpaks are similar, but not the same.


The equipment change does not involve a change in operating principle or design, and therefore would be considered a level 1 SUPAC IR manufacturing change. However, there is a difference in the blister packages. The sponsor will need to demonstrate both the equivalency between the two blister packages and equal stability between the drug product in the two blister packages. Thus the sponsor's commitment to placing the first production batch of the product on long term stability testing and reporting the results in the annual report is not considered to be adequate.

**18. CONCLUSIONS AND RECOMMENDATIONS:**  
This CBE Supplement is approvable pending satisfactory resolution of the issues delineated in the draft letter.

<b>19. REVIEWER NAME</b> David T. Lin, Ph.D. Review Chemist	<b>SIGNATURE</b>  5/10/99	<b>DATE COMPLETED</b> 10-MAY-1999
---	--	--------------------------------------

cc: Original: NDA 19-697/SCM-016  
HFD-580/Division File  
HFD-580/JMercier  
HFD-580/MRhee/DLin

INIT by MJ Rhee

 5/10/99

Filename: S19697.016 (doc)

**Draft Letter**

The review of the CMC information submitted for NDA 19-653/S-021 has been completed and the following comments and requests should be submitted to the sponsor:

1. Provide the following long term stability data on the drug product which has been packaged in the new blister pack: 1) 18 months on one batch at 25°C/60% RH and 2) 12 months on two batches at 25°C/60% RH.
2. Provide the results of the leak testing on the new empty blister packs.
3. Commit to provide the following additional stability data: 1) 24 months on one batch at 25°C/60% RH and 2) 18 months on two batches at 25°C/60% RH.

OCT 22 1999

**CHEMIST REVIEW #2  
OF SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 19-697/SCM-016
3. **SUPPLEMENT NUMBERS/DATES:**  
**Letterdate:** 10-NOV-1998  
**Stampdate:** 12-NOV-1998
4. **AMENDMENTS/REPORTS/DATES:**  
**Letterdate:** 01-JUL-1999  
**Stampdate:** 02-JUL-1999
5. **RECEIVED BY CHEMIST:** 12-JUL-1999

**6. APPLICANT NAME AND ADDRESS:**

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

**1. NAME OF DRUG:**

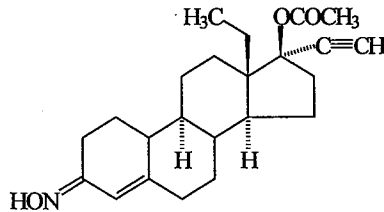
Ortho Tri-Cyclen Tablets

**2. NONPROPRIETARY NAME:**

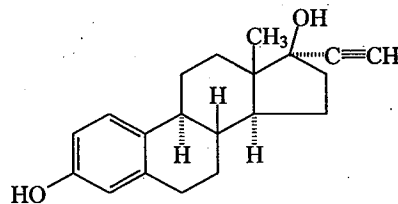
Norgestimate/ethinyl estradiol (NGM/EE)

**3. 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 $\alpha$ )



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

Tablet

**5. POTENCY:**

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

**6. PHARMACOLOGICAL CATEGORY:**

Progestin, estrogen/Contraception

**7. HOW DISPENSED:**

RX

**8. RECORDS & REPORTS CURRENT:**

Yes

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

NDA 19-653/SCM-0271

**10. SUPPLEMENT PROVIDES FOR:**

Change in packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle.

**11. COMMENTS**

The company will be replacing the current Dialpak Tablet Dispenser with Dialpak III Tablet Dispenser. This involves the replacement of the current packaging equipment with new equipment. The new equipment is a newer version of the currently used equipment and the packaging operation will remain the same. In addition the same [ ] and aluminum foil will be used for the blister package. The blister packages from the two dialpaks are similar, but not the same.

The equipment change does not involve a change in operating principle or design, and therefore would be considered a level 1 SUPAC IR manufacturing change. However, there is a difference in the blister packages. The sponsor will need to demonstrate both the equivalency between the two blister packages and equal stability between the drug product in the two blister packages. Thus the sponsor's commitment to placing the first production batch of the product on long term stability testing and reporting the results in the annual report is not considered to be adequate.

In the July 1, 1999 amendment the sponsor has responded to the May 12, 1999 FDA approvable letter. See the review notes section for more detailed comments.

**12. CONCLUSIONS AND RECOMMENDATIONS:**

This CBE Supplement may be approved. Issue an approval letter.

**13. REVIEWER NAME**

David T. Lin, Ph.D.  
Review Chemist

**SIGNATURE**

*David T. Lin*  
10/21/99

**DATE COMPLETED**

21-OCT-1999

cc: Original: NDA 19-697/SCM-016

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

INIT by MJ Rhee

*MJRhee 10/21/99*

Filename: S19697BC.016 (doc)

1 Page(s) Withheld

Chemistry Review #2 (19-697/S-016)

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-653/S-021 & 19-697/S-016**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**





ORIGIMATE

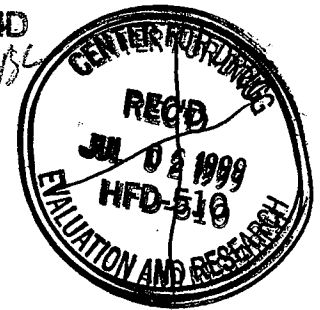
NDA SUPP AMEND

S-026-04

THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

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

JUL - 1 1999



Dr. Lisa Rarick  
U.S. Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and  
Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
Attn: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, MD 20857

~~NDA 19-653~~ (S-021)  
ORTHO-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

Please cross-refer to:

~~NDA 19-697~~ (S-016)  
ORTHO TRI-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

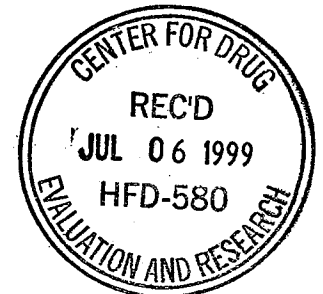
Amendment to Special  
Supplements – Changes Being  
Effected

Dear Dr. Rarick:

Reference is made to our approved New Drug Application for ORTHO-CYCLEN Tablets NDA 19-653, and ORTHO TRI-CYCLEN Tablets NDA 19-697, our norgestimate/ethinyl estradiol containing oral contraceptive products. Further reference is made to the above referenced Special Supplements – Changes Being Effected dated 10 November 1998 (copy attached) which provided for a change in packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle.

We further refer to your letter dated 12 May 1999 (copy attached) in which you advise that these applications are approvable with the provision that we:

1. Provide the following long-term stability data of the drug product which has been packaged in the new blister pack:
  - a) 18-months on one batch at 25 °C/60% RH, and
  - b) 12-months on two batches at 25 °C/60% RH.
2. Provide the results of the leak testing on the new empty blister packs.
3. Commit to provide the following additional stability data:
  - c) 24-months on one batch at 25 °C/60% RH, and
  - d) 18-months on two batches at 25 °C/60% RH.



As outlined in our letter of 21 May 1999 (copy attached), we are hereby submitting the following information which we committed to supply for each of the referenced supplemental NDAs to support approval of these applications:

1. Stability Data:

- a) 12-months on one batch of ORTHO-CYCLEN at [ ] °C/[ ]% RH  
(Batch 18H100)
- b) 12-months on one batch of ORTHO TRI-CYCLEN at [ ] °C/[ ]% RH  
(Batch 18D594)
- c) 18-months on one batch of ORTHO -CYCLEN at [ ] °C/[ ]% RH  
(Batch 18G596)
- d) 18-months on one batch of ORTHO TRI-CYCLEN at [ ] °C/[ ]% RH  
(Batch 27M058B)

2. Leak testing results on the new empty blister packs.

Please be advised that stability testing was carried out at [ ] °C/[ ]% RH as specified in our NDA. The additional requested stability results will be provided on or before 1 January 2000.


We trust that this amendment will fulfill the requirements set forth in your letter of 12 May 1999.

In accordance with 21 CFR Part 314.70 (a), identical field copies of this correspondence have been filed with our local FDA District Offices.

Should you have any questions or comments concerning this submission, 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

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

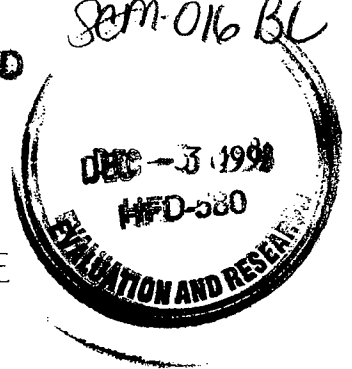
*[Handwritten initials and date]*

Field Copy: Newark District Office, North Brunswick  
San Juan District Office, San Juan, Puerto Rico



NDA SUPP AMEND

*SJM-016 BL*



THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

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

*Reviewed  
See Chem. Rev.  
and w/ 5/10/99  
DTC  
5/24/99*

DEC 02 1998

Lisa Rarick, M.D., Director  
Division of Reproductive and Urologic  
Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II, HFD-580  
Attn.: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

SUPAC IR Guidance  
Section VI.A. Level 1

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

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

Response to Agency Request

Dear Dr. Rarick:

Reference is made to our approved NDA's, 19-653 (ORTHO-CYCLEN Tablets) and 19-697 (ORTHO TRI-CYCLEN Tablets) and our SUPAC IR submission dated November 10, 1998 (S-021 ORTHO-CYCLEN Tablets, S-016 ORTHO TRI-CYCLEN Tablets).

Further reference is made to a telephone conversation on November 23, 1998 between Dr. David Lin of your Division and Donna Panasewicz of The R.W. Johnson Pharmaceutical Research Institute in which Dr. Lin requested a sample of both the current DIALPAK blister package and the DIALPAK III blister package.

At this time, we are submitting two each of the above requested samples.

Field copies of this submission are being forwarded directly to the San Juan and Newark District Offices. We certify that the filed copies are true copies of the information contained in the archival and review copies of this supplemental application.

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
CSO INITIALS	DATE	

*[Handwritten signature and date over the form]*

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.

Sincerely yours,

The R.W. Johnson  
Pharmaceutical Research Institute



Donna M. Panasewicz  
Manager  
Regulatory Affairs

Enclosure



Food and Drug Administration  
Rockville MD 20857

NDA 19-697/S-016

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

NOV 20 1998

Attention Donna Panasewicz,  
Manager, Regulatory Affairs

Dear Ms. Panasewicz:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ortho Tri-Cyclen

NDA Number: 19-697

Supplement Number: S-016

Date of Supplement: November 10, 1998

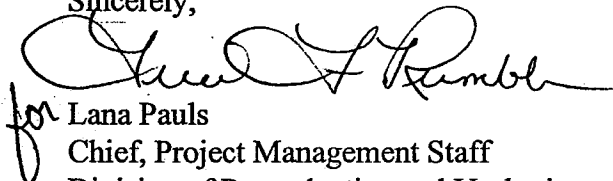
Date of Receipt: November 12, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 11, 1999 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 Reproductive and Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
Attention: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely,



for Lana Pauls  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 19-697/S-016

Page 2

cc:

Original NDA 19-697/S-016

HFD-580/Div. Files

HFD-580/CSO/Kish,C

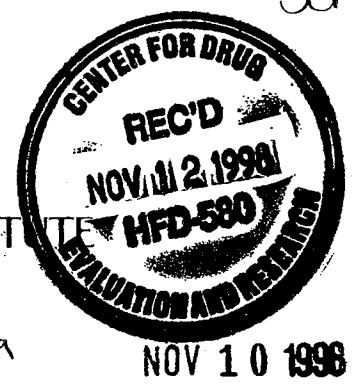
SUPPLEMENT ACKNOWLEDGEMENT

SCM-016

**ORIGINAL**

NDA NO: 19 697 REF NO: SCM-016  
NDA SUPPL FOR CMY (SI)

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



*See Chem. Rev. dated 5/10/99  
DTC 5/10/99*

Lisa Rarick, M.D., Director  
Division of Reproductive and Urologic  
Drug Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II, HFD-580  
Attn.: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

**SUPAC IR Guidance**  
**Section VI.A. Level 1**

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

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

Dear Dr. Rarick:

Reference is made to our approved NDA's, 19-653 (ORTHO-CYCLEN Tablets) and 19-697 (ORTHO TRI-CYCLEN Tablets).

Reference is also made to our General Correspondence dated 04 October 1995 (Attachment 1), which detailed our plans for a change in packaging equipment, pertinent to the above noted products and to a letter addressed to Dr. Marilyn Apfel dated 28 March 1996 (Attachment 2), requesting guidance and interpretation of the SUPAC guidelines. Specifically, if the SUPAC IR Guidelines apply to a change in packaging equipment in which the current packaging equipment utilized would be replaced with a newer version of the same basic operating design and principle. On 01 May 1996, a response to our request was received from Dr. Apfel (Attachment 3), in which it was confirmed that this type of change would be covered under SUPAC IR.

As this time, we wish to inform the Agency that we are instituting the change in packaging equipment for the previously noted products 30 days from your receipt of this letter. We wish to note that initially these products will be utilized for a market test of the DIALPAK III compact, (limited distribution of the product in an isolated area) with an official launch anticipated mid February 1999. In accordance with the SUPAC IR Guidance, we commit to place one batch of each product on long term stability and will report the results in the annual report for each product. In addition, we have also placed one lot of ORTHO-NOVUM® 7/7/7 Tablets on accelerated stability as had been requested by Dr. Rhee of your Division in a previous conversation on this subject. As was agreed with Dr. Rhee, the results of this stability study will be reported in the annual report for this product. It is anticipated that ORTHO-NOVUM® 7/7/7 will be launched in 1999. Prior to its launch, a separate SUPAC supplement will be submitted.

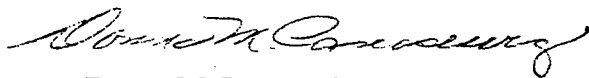
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Field copies of this submission are being forwarded directly to the San Juan and Newark District Offices. We certify that the field copies are true copies of the information contained in the archival and review copies of this supplemental application.

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.

Sincerely yours,

The R.W. Johnson  
Pharmaceutical Research Institute



Donna M. Panasewicz  
Manager  
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE





THE R.W. JOHNSON  
PHARMACEUTICAL RESEARCH INSTITUTE

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

ORIGINAL

NDA SUPP AMEND

S-016 *henc*

MAY 21 1999

Dr. Lisa Rarick  
U.S. Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and  
Urologic Drug Products, HFD-580  
Office of Drug Evaluation II  
Attn: Document Control Room 14B-03  
5600 Fishers Lane  
Rockville, MD 20857

**NDA 19-653 (S-021)**  
ORTHO-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

**Please cross-refer to:**

**NDA 19-697 (S-016)**  
ORTHO TRI-CYCLEN® Tablets  
(norgestimate/ethinyl estradiol)

**Intent to Amend Special  
Supplements – Changes  
Being Effectuated**

*Reviewed  
The sponsor's  
commitment is  
satisfactory.  
DTS  
5/27/99*

*NO FOR  
SP27/99*

Dear Dr. Rarick:

Reference is made to our approved New Drug Application for ORTHO-CYCLEN Tablets NDA 19-653, and ORTHO TRI-CYCLEN Tablets NDA 19-697, our norgestimate/ethinyl estradiol containing oral contraceptive products. Further reference is made to the above referenced Special Supplements – Changes Being Effectuated dated 10 November 1998 (copy attached) which provided for a change in packaging equipment in which the current equipment is replaced with a newer version of the same basic operating design and principle.

We further refer to your letter dated 12 May 1999 (copy attached) in which you advise that these applications are approvable with the provision that we:

1. Provide the following long-term stability data of the drug product which has been packaged in the new blister pack:
  - a) 18-months on one batch at 25 °C/60% RH, and
  - b) 12-months on two batches at 25 °C/60% RH.
2. Provide the results of the leak testing on the new empty blister packs.
3. Commit to provide the following additional stability data:
  - c) 24-months on one batch at 25 °C/60% RH, and
  - d) 18-months on two batches at 25 °C/60% RH.

*NAT  
JML 5/28/99*

In accordance with 21 CFR 314.120, we wish to notify you of our intent to file an amendment to each of the referenced supplemental NDAs to support approval of these applications. At this time we hereby commit to:

1. Provide the following stability data on or before 1 July 1999:
  - a) 12-months on one batch of ORTHO-CYCLEN at [ ] °C/[ ]% RH \*
  - b) 18-months on two batches of ORTHO TRI-CYCLEN at [ ] °C/[ ]% RH\*
2. Provide the leak testing results on or before July 1, 1999
3. Provide the additional stability results on or before 1 January 2000.

\*Please be advised that current stability NDA requirements for storage are [ ] °C/[ ]% RH.

We trust that the above will fulfill the requirements set forth in your letter of 12 May 1999.

In accordance with 21 CFR Part 314.70 (a), identical field copies of this correspondence has been filed with our local FDA District Offices.

Should you have any questions or comments concerning this submission, 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

Field Copy: Newark District Office, North Brunswick  
San Juan District Office, San Juan, Puerto Rico