# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# 19-653/S-018 & 19-697/S-013

***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:*** 08/21/1996

***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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-653/S-018 & 19-697/S-013

## 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) | X |
| 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-018 & 19-697/S-013**

# APPROVAL LETTER

15-1 ORIGINAL

NDA 19-653/S-018
NDA 19-697/S-013

AUG 21 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 June 28, 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.

We also refer to your correspondence dated July 2, 1996.

These supplemental applications provide for a revised dissolution method using a medium with increased Tween 20 concentration (from 0.025% to 0.05%), with an interim specification of Q=80% at 20 minutes for one year.

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 8/21/96

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

cc:
Orig. NDA's (2)
HFD-580(2)
DISTRICT OFFICE
HFD-80
HFD-580/HDavies/MRhee
HFD-580/CKish/8.21.96/n19653ap.s18
concurrences:LPauls 8.21.95/MRhee 8.21.96/HDavies 8.21.96

SUPPLEMENT APPROVAL (S/AP)

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**19-653/S-018 & 19-697/S-013**

## CHEMISTRY REVIEW(S)

ORIGINAL

CHEMIST'S REVIEW

**1. Organization** DMEDP HFD-510 15-1

**2. NDA Number** 19-697

AUG 21 1996

**3. Name amd 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-013
6-28-96

**5. Name of Drug**
Ortho Tri-Cyclen

**6. Nonproprietary Name**
Norgestimate/EE tablets

**7. Supplement Provides For**
The revised dissolution method using a medium with increased Tween 20 concentration (from 0.025% to 0.05%), with an interim specification of Q=80% at 20 minutes for one year.

**8. Amendment**
7-2-96

**9. Pharmacological Category**
Oral contraceptive

**10. How Dispensed**
RX

**11. Related**
NDA 19-653 (S-018)

**12. Dosage form**
Tablets for oral administration

**13. Potency**
180/35, 215/35, 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 supplement was submited for approval of increasing Tween 20 concentration in the dissolution medium from 0.025% to 0.05% with other dissolution parameters intact. The amendment dated 7-2-96 was submitted to correct several misstatements on the mutual agreements (#2 and #3 in p. 2 and a statement on the review deadline) in the cover letter of the supplement. The change of Tween 20 concentration proposed in the supplement was triggered by the firm after they had encountered situations where some recent batches as well as a stability batch did not pass the dissolution test. The firm has provided explanation for the problem and concluded that increasing the Tween 20 concentration to 0.05% with Q=80% @30 minutes may be a possible solution. Although increasing the Tween concentration to 0.05% is acceptable, Q=80% @30 minutes is deemed not acceptable. Eventually, the firm agreed to implement this new concentration (0.05%) with other dissolution parameters intact on an interim basis for one year. This supplement contains the following information:

Attachment I: A general correspondence background document
Attachment II: Dissolution data requested by Division of Biopharmaceutics
Attachment III: Further data requested by this reviewer
Attachment IV: S1 failure data of batches analyzed during the investigation

**16. Conclusion and Recommendation**
Division of Biopharmaceutics did not object to the interim dissolution specification (Q=80% @20 minute) with 0.05% Tween 20 (See Biopharm's review dated 8-20-96 and Chem Rev #1 dated 8-21-96 of S-018, NDA 19-653, for detail). Issue an approval letter.

**17. Name** Moo-Jhong Rhee, Ph.D.

**Reviewer's Signature**

**Date** 8-21-96

**Distribution** **Original Jacket** **Reviewer/CSO** **Division File**

**R/D initialed by**
SL.258 H. Davis 8/21/96

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**19-653/S-018 & 19-697/S-013**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

15-1

AUG 20 1996 ORIGINAL

# *CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW*

## *Division of Pharmaceutical Evaluation II*

**NDA 19-653**
Supplement Serial No. 018
ORTHO-CYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

**SUBMISSION DATE:** June 28, 1996

**NDA 19-697**
Supplement Serial No. 013
ORTHO-TRICYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

The R.W. Johnson Pharmaceutical Res. Inst.
Div. of Ortho Pharmaceutical Corp.
Raritan, New Jersey

**REVIEWER:** Angelica Dorantes, Ph.D.

**TYPE OF SUBMISSION:** Supplements- Changes Being Effected/Dissolution **Code: 3 S**

**SYNOPSIS:**

Reference is made to NDA 19-653 for ORTHO-CYCLEN® and to NDA 19-697 for ORTHO-TRICYCLEN®. Reference is also made to a teleconference between Dr. Moo Jhong Rhee of FDA and Donna Panasewicz of the R.W. Johnson Pharmaceutical Research Institute on June 21, 1966 in which the sponsor agreed to the following:

1. Acceptance of an interim specification of Q=80% at 20 minutes using 0.05% TWEEN 20 for one year.
2. Collection of dissolution data (informational purposes) for one year at 15 minutes in addition to the 20 minutes.
3. Continuation of their investigation into the low results on Batches 16A632 through 16D639 and provide FDA with an explanation for the low results in one year.

In addition, Dr. Rhee requested that all correspondence previously submitted to the agency relating to this issue be included in this submission. Therefore, the following information was included in Attachments I to IV of the submission:

***Attachment I*** - A general correspondence background document which was sent to FDA on June 6, 1996.

***Attachment II*** - Dissolution data using 0.05% TWEEN 20 concentration at 30 and 60 minute intervals which was sent to FDA via Fax on June 14, 1996.

***Attachment III*** - Information on the sponsor's current level of S2 testing for Dissolution Method No. DM91-020, TWEEN 20 at a concentration of 0.025% at 20 minutes.

*Attachment IV* - Information providing the S1 failure rates for lots which were included in a "round robin study".

At this time the sponsor is submitting Supplement Serial No. 018 for NDA 19-653 for ORTHO-CYCLEN® and Supplement Serial No. 013 for NDA 19-697 for ORTHO-TRICYCLEN® dated June 28, 1996. Due to the fact that the currently used dissolution medium causes variability in the norgestimate dissolution results, in these supplements the sponsor is requesting the change of the concentration of the dissolution medium used in Dissolution Method No. DM 91-020 for ORTHO-CYCLEN® and ORTHO-TRICYCLEN® as follows:

**FROM:** Dissolution Medium - 0.025% TWEEN 20

**TO:** Dissolution Medium - 0.050% TWEEN 20

**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed Supplement Serial No. 018 for NDA 19-653 for ORTHO-CYCLEN® and Supplement Serial No. 013 for NDA 19-697 for ORTHO-TRICYCLEN® dated June 28, 1996. OCPB/DPEII considers that the sponsor's proposed change for the dissolution medium from 0.025% TWEEN 20 to 0.050% TWEEN 20 is appropriate and this change is acceptable.

In this document the sponsor agrees to the conditions put forth by Dr. Rhee with regard to the testing intervals and continuance of their investigations for one year following the approval of these supplements. OCPB/DPEII acknowledges the sponsor commitment to provide one-year additional dissolution data. Based on these results, the Agency will revise/update as appropriate the dissolution method and specification for ORTHO-CYCLEN® and ORTHO-TRICYCLEN®.

Please convey Recommendation as appropriate to the sponsor.

---

Dorantes 8/20/96

Angelica Dorantes Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John P. Hunt JPH 8/20/96

FT Initialed by John P. Hunt 8/20/96

cc: NDA 19-653 & 19-697, HFD-580 (Kish, MO), HFD-870 (M. Chen, Dorantes), HFD-870 for C. Bott (Drug, Chron, and Reviewer), HFD-205 (FOI).

151

# ORIGINAL

MAY 30 1996

## *CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW*
### *Division of Pharmaceutical Evaluation II*

**NDA 19-653**
Supplement Serial No. 016
ORTHO-CYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

**SUBMISSION DATE:** April 1, 1996

**NDA 19-697**
Supplement Serial No. 011
ORTHO-TRICYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

The R.W. Johnson Pharmaceutical Res. Inst.
Div. of Ortho Pharmaceutical Corp.
Raritan, New Jersey

**REVIEWER:** Angelica Dorantes, Ph.D.

**TYPE OF SUBMISSION:** Supplement- Changes Being Effected/Dissolution Data **Code: 3 S**

**SYNOPSIS:**

Reference is made to Supplement Serial No. 009 for NDA 19-653 for ORTHO-CYCLEN® and to Supplement Serial No. 002 for NDA 19-697 for ORTHO-TRICYCLEN® submitted on July 26, 1993, which provided for a new non-alcoholic based dissolution method, (DM91-020). Reference is also made to the Agency's letter dated February 16, 1995 in which FDA stated that before a final dissolution method and specification were accepted, the Agency would like to see the additional dissolution data accrued for one year using the proposed dissolution method; USP Apparatus II (paddle), 600 mL of 0.025% Tween 20 in water, **i)** at 75 rpm and **ii)** at 15 and 20 minutes sampling times.

At this time the sponsor is submitting Supplement Serial No. 016 for NDA 19-653 for ORTHO-CYCLEN® and Supplement Serial No. 011 for NDA 19-697 for ORTHO-TRICYCLEN® dated April 1, 1996. In these supplements the sponsor is including their proposed final dissolution specifications for Norgestimate and Ethinyl Estradiol applicable to both product release and stability testing. The proposed specifications are as follows:

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

Also, reference is made to a meeting held at the Agency on September 14, 1995 in which was discussed the variability of the dissolution results using Dissolution Method DM 91-020 for Norgestimate/Ethinyl

Estradiol Tablets. In this submission the sponsor is pointing-out that they continue experiencing variability in the dissolution results and the investigation into the reason for this variability as well as the increase in S2 testing since employing this method is on-going. Upon completion of their investigation the sponsor plans to discuss with the Agency their findings and future steps.

**RECOMMENDATION:**

In a telephone conversation on April 20, 1996 with Ms. Donna M. Panasewicz of R.W. Johnson, it was learned that the sponsor is planing to present on June 19, 1996 (FDA meeting), an update of the dissolution results for Norgestimate/Ethinyl Estradiol Tablets using the dissolution method DM 91-020. Also, in this meeting they will present their results for the on-going investigation into the reason for the dissolution variability as well as the increase in S2 testing since employing this method and perhaps they will propose new dissolution specifications.

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) would like to review the new dissolution information that will be presented by R.W. Johnson in the coming June 19th meeting before setting the proposed dissolution specifications for product release and stability testing for Norgestimate and Ethinyl Estradiol using Method DM 91-020 [USP Apparatus II (paddle), 600 mL of 0.025% Tween 20 in water, at 75 rpm]. At this time OCPB/DPEII recommends that for product release and stability testing, the sponsor keep using method DM 91-020 and currently approved interim dissolution specifications of Q=80% at 20 minutes for both Norgestimate and Ethinyl Estradiol.

Please convey Recommendation as appropriate to the sponsor.

---

5/28/96

Angelica Dorantes Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by Mei-Ling Chen. JPH 5/28/96

FT Initialed by Mei-Ling Chen. 5/29/96

cc: NDA 19-653 & 19-697, HFD-510 (CSO, MO), HFD-870 (M. Chen, Dorantes), HFD-870 for C. Bott (Drug, Chron, and Reviewer), HFD-205 (FOI).

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**19-653/S-018 & 19-697/S-013**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA NO. 19697 REF. NO. 003

NDA SUPPL FOR SCS

ORIGINAL

NDA SUPPLEMENT

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

JUN 28 1996

Lisa Rarick, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
HFD #580
Document Control Room 14B-03
5600 Fischers Lane
Rockville, Maryland 20857

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

**Please cross-refer to:**

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

**SUPPLEMENTAL APPLICATION**
**EXPEDITED REVIEW REQUESTED**

Dear Dr. Rarick:

Reference is made to our NDA's 19-653 for ORTHO-CYCLEN Tablets and 19-697 for ORTHO TRI-CYCLEN Tablets respectively. At this time we submit herewith a supplement and request expedited approval to change the concentration of the medium used in our Dissolution Method, DM 91-020, for ORTHO-CYCLEN and ORTHO TRI-CYCLEN Tablets as follows:

From: Dissolution Medium - 0.025% TWEEN 20
To: Dissolution Medium - 0.050% TWEEN 20

This change is necessitated by the fact that 0.025% TWEEN 20 dissolution medium causes variability in the norgestimate dissolution results. This variability was identified during an exhaustive investigation which we conducted over the past year. The investigation included the following:

- Critical Process Parameter Experiments
- Raw Material Review including the active ingredients and excipients
- Batch Record Review
- Laboratory Data Review
- Dissolution Method Investigation

letter ok 6/27/96

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 01 1996
HFD-510

Reference is also made to a telephone conversation between Dr. Moo Jhong Rhee of your division and Donna Panasewicz of the R.W. Johnson Pharmaceutical Research Institute on June 21 1996, in which Dr. Rhee agreed to this revision provided that we commit to the following:

1. We agree to accept an interim specification of Q=80% at 20 minutes using 0.050% TWEEN 20 for one year.

2. We agree to collect dissolution data at 15 minutes in addition to the 20 minutes for one year for informational purposes.

3. We agree to continue our investigation into the low results on Batches 16A632 through 16D639 and to supply FDA with an explanation for the low results in one year. Upon approval of this supplement final disposition of these batches will be determined using 0.050% TWEEN 20 as the dissolution medium.

In addition, Dr. Rhee requested that all correspondence previously submitted to the Agency relating to this issue be supplied as part of this submission. The correspondence is attached as noted below. Contained in these attachments are several data points which are asterisked(*). The asterisks indicate a change to the data due to typographical errors from that which was previously sent to the Agency. These errors were detected during our 100% audit of all data points. We certify that all data contained in this document are accurate at this time and these changes have no impact on our conclusions.

**Attachment I** - A General Correspondence Background Document which was sent to FDA on June 6, 1996.

**Attachment II** - Data which was faxed to Dr. A Dorantes and Mr. J. Hunt on June 14, 1996 following a telephone conference between them and representatives from ORTHO-McNeil and The R.W. Johnson Pharmaceutical Research Institute (OMP/PRI) on June 13, 1996. It was during that conversation that they requested that we send to them any data which we had on dissolution testing using the 0.050% TWEEN 20 concentration at 30 and 60 minute intervals.

**Attachment III** - Data requested by Dr. Moo Jhong Rhee during a telephone conversation on June 14, 1996. Specifically he requested information with regard to our current level of S2 testing for Dissolution Method DM91-020, TWEEN 20 at a concentration of 0.025% at 20 minutes.

**Attachment IV** - Data requested by Dr. Moo Jhong Rhee during a telephone conversation on June 20, 1996 . The data requested by Dr. Rhee were the S1 failure rates for lots which were included in a "round robin study" as part of our investigation.For ease of review the results of the "round robin study" are also included in this attachment.

As discussed with Dr. Rhee on June 21, 1996, we hereby agree to commit to the conditions put forth with regard to the testing intervals and continuance of our investigation and will apprise the Agency in one year following the approval of this supplement. It was also our understanding from this conversation that this supplement will be reviewed within 30 days.

A field copy of this submission is being forwarded directly to the FDA Newark District Office and to the San Juan, Puerto Rico District Office. We certify that the field copies are true copies of the information contained in the archival and review copies of this supplemental application.

We trust that all of Dr. Rhee's requirements have been addressed in this supplement. Should you have any questions, you may contact me at (908) 704-4600 a number designated for FDA use, 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
Regulatory Affairs Manager

DMP:gg
Enc.

cc: Dr. Moo Jhong Rhee - Desk Copy
Dr. A. Dorantes - Desk Copy
Mr. J. Hunt - Desk Copy

N:\DONNA\RARICK

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUL 10 1996

NDA No. 19-697

R.W. JOHNSON PHARMACEUTICALS RESEARCH INSTITUTE
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: ORTH TRI-CYCLEN(Norgestimate + Ethinyl Estradiol)

NDA Number: 19-697

Supplement Number: S-013

Date of Supplement: JUNE 28, 1996

Date of Receipt: JULY 1, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on AUG 30 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