CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-697/S-004

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: 12/28/1994

Indications: For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraceptives.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-004

CONTENTS

Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-004

APPROVAL LETTER

NDA 19-697/S-004

DEC 28 1994

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

Dear Ms. Drzewiecki:

Please refer to your May 5, 1994, 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.

This supplemental application provides for two new packaging facilities at the manufacturing site in Manati, Puerto Rico.

We have completed the review of this supplemental application and it is 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 Dr. Stockbridge at 310-443-3520.

Sincerely yours,

12-27-94

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc:
Arch NDA
HFD-510
DISTRICT OFFICE
HFD-426\ADorantes
HFD-80
HFD-510\RBennett\YChiu\MRhee\KRaheja\EGalliers
HFD-510\LStockbridge/12.19.94\N19697ap.S04 12-22-94

Concurrences: MRhee 12.19/YChiu 12.20/EGalliers 12.21.94

SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-510

2. NDA Number
19-697

DEC 13 1994

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-004
5-5-94

ORIGINAL

5. Name of Drug
Ortho-TriCyclen

6. Nonproprietary Name
Norgestimate/EE tablets

7. Supplement Provides For
Two new packaging facilities at Manati in Puerto Rico

8. Amendment

9. Pharmacological Category
Oral contraceptive

10. How Dispensed
RX

11. Related
IND/NDA/DMF
NDA 19-653

12. Dosage form
Tablets for oral administration

13. Potency
180/35, 215/35, 250mcg/35mcg
(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: $C_{20}H_{24}O_2$ MW: 296.41

15. Comments

This supplement was submitted for a new packaging site, Johnson & Johnson Pharmco Inc., Manatii, Puerto Rico. This firm was originally named as Ortho Pharmaceuticals, Inc. and later renamed as above on 4-21-94. It has two facilities (it is called as *original* and *new*). The *original* facility is involved in manufacturing the Ortho Tri-Cyclen tablets which has been packaged at the facility in Raritan. (This *original* facility is also involved in manufacturing and packaging Ortho-Cyclen tablets). Now the firm proposes to package the Ortho Tri-Cyclen tablets at the *original* and *new* facilities (the *new* facility also packages Ortho Cyclen tablets). (cont'd)

16. Conclusion and Recommendation

EER was rated acceptable on 5-20-94 and updated on 12-5-94. The issues on the new dissolution method will be dealt through the pending supplement (S-002). Therefore, from the chemistry point of view, this supplement is approvable. Issue an approval letter.

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

Reviewer's Signature

Date
12-13-94

Distribution **Original Jacket** **Reviewer** **Division File**

R/D initialed by 12/18/94

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review

19-697/S-004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

RECEIVED MAY 17 1994

S

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)	DATE	PHONE NO.	EER ID #
☒ Original ☐ Follow-Up ☐ FUR	5-16-94	443-3520	6394

REQUESTOR'S NAME	DIVISION	MAIL CODE
Moo-Jhong Rhee	DMEPP	HFD-510

APPLICATION AND SUPPLEMENT NUMBER: 19-697, S-004

BRAND NAME	ESTABLISHED NAME
Ortho Tri-Cyclen	Norgestimate / Ethinyl Estradiol

DOSAGE AND STRENGTH	STERILE
180μg/35μg, 210μg/35μg, 250μg/35μg	☐ YES ☒ NO

PROFILE CLASS	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)
TCM	3S

APPLICANT'S NAME: R.W. Johnson Pharmaceutical Research Institute

ADDRESS: Route 202, P.O. Box 300
Raritan, New Jersey 08869

COMMENTS: There are two identical buildings; one was previously approved for packaging, the other is to be inspected. The two have identical equipment sequence.

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. Ortho Pharmaceuticals, Inc Road No. 2 - Km 45.6 Bo. Campo Alegre Manati, Puerto Rico 00674	packaging	3454	OR PM	
2.				
3.				
4.				
5.				

FOR HFD-324 USE ONLY	CSO	DATE RECEIVED
	Melissa H. Yee	MAY 20 1994
	CGMP COMPLIANCE STATUS	DATE
	Acceptable	5/20/94

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

V

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One) ☐ Original ☐ Follow-Up ☒ FUR	DATE 11-21-94	PHONE NO. 443-3520	EER ID # 11/94
REQUESTOR'S NAME Moo-Jhong Rhee, Ph.D.		DIVISION DMEDP	MAIL CODE HFD- 510
APPLICATION AND SUPPLEMENT NUMBER 19-697, S-004		User Fee Due Date 11/6/94	
BRAND NAME Ortho Tri-Cyclen		ESTABLISHED NAME Norgestimate/Ethinyl Estradiol	
DOSAGE AND STRENGTH 180mg/35mg, 210/35, 250/35mg			STERILE ☐ YES ☒ NO
PROFILE CLASS TCM		PRIORITY CLASSIFICATION (See SMG CDER-4820.3) 3S	
APPLICANT'S NAME R.W. Johnson Pharmaceutical Research Institute			
ADDRESS Route 202, P.O. Box 300 Raritan, New Jersey 08869			
COMMENTS The review of this supplement is to be done soon. Could you update this EER ASAP? (Original EER attached) ID# 6399			

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	F KEY/ CIRTS ID	HFD-324 USE ONLY
1. Ortho Pharmaceuticals, Inc. Road No. 2-Km 45.6 Bo. Campo Alegre	packaging	3454		
2. Manati, Puerto Rico 00674				
3.				
4.				
5.				

FOR HFD-324 USE ONLY		
CSO	Mercedes Aragon	DATE RECEIVED 11/25/94
COMP/COMPLIANCE STATUS	Acceptable	DATE 12/5/94

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

13.1

DEC 14 1994

NDA 19-697 ✓

SUBMISSION DATE: May 5, 1994

ORTHO TRI-CYCLEN® Tablets
Norgestimate/Ethinyl Estradiol
The R.W. Johnson Pharmaceutical Res. Inst.
Div of Ortho Pharmaceutical Corp.
Raritan, New Jersey

ORIGINAL

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Dissolution Data to Support Additional Packing Site **Code: 3 S**

SYNOPSIS:

The sponsor is submitting a supplement to NDA 19-697 for ORTHO TRI-CYCLEN® Tablets (norgestimate/ethinyl estradiol). In accordance with the provisions of 21CFR 314.70(b)(2)(vi), the sponsor is submitting this supplemental application to allow Johnson & Johnson Pharmaco (P.R.) Inc., Manati, Puerto Rico as an additional site for the packaging of ORTHO TRI-CYCLEN® Tablets.

In support of this supplement, the sponsor included Chemistry, Manufacturing, and Control information which includes 6-month stability data on three batches each of the 180 µg norgestimate/35 µg EE, and 215 µg norgestimate/35 µg EE strength tablets. The 250 µg norgestimate/35 µg strength tablets are currently packed at Puerto Rico as well as the monophasic product ORTHO CYCLEN®

On November 22, 1994, the Division of Biopharmaceutics was consulted by Dr. Moo-Jhong Rhe, reviewing chemist from HFD-510, regarding the comparative dissolution information included in the Supplement to 19-697 dated May 5, 1994. In these studies, dissolution testing was conducted to compare the dissolution methods on ORTHO TRI-CYCLEN® Tablets using the original hydro-alcoholic method (PD 1818) and the new surfactant method (DM 91-020). The main objective was to demonstrate the equivalence of the dissolution methods.

Dissolution profiles were generated for the 180/35 (SRN 7473, 5°C 180 days), 215/35 (SRN 7440, 5°C 180 days) and 250/35 (Lot 130544, initials from production) tablets using both methods. Also, stability samples of SRN 7473 and SRN 7440 (30°C, 160 days) were tested with both methods with sampling at 30 minutes. The methods are summarized below:

	PD 1818: Old Method	**DM 91-020: New Method**
Apparatus:	Apparatus 1, 125 rpm	Apparatus II, 75 rpm
Dissolution Medium:	13% isopropyl alcohol in water, 900 mL	0.0255 Tween 20, 600 mL

The dissolution profiles of ORTHO TRI-CYCLEN® (180/35, 215/35 and 250/35) Tablets are presented in Figures 1 to 3. The results indicate that the two dissolution methods produce comparable dissolution profiles for norgestimate and EE. Figure 4 presents the results from the stability samples (180/35 and 215/35). For the stability samples, both methods produce comparable results at 30 minutes. Figures 1 to 4 and individual dissolution data are included in Attachment I.

In addition, it should be noted that on August 23, 1994 the sponsor submitted a supplement to NDA 19-697 for ORTHO-TRI-CYCLEN® Tablets. In that supplement reference was made to a previous supplemental application dated July 26, 1993, which provided information for a new non-alcoholic based dissolution method (DM 91-020), and to an FDA not-approvable letter dated May 6, 1994, which listed the deficiencies for the July 26, 1993 supplemental application. In the August 23, 1994 supplement to NDA 19-697, the sponsor included their responses to the Biopharm Deficiencies outlined in the May 6, 1994 Agency's letter. Based upon the review of the dissolution data submitted in the August 23, 1994 supplement, the Division of Biopharmaceutics accepted the sponsor's proposed tentative specification of Q = 80% at 20 minutes for both norgestimate and ethinyl estradiol (USP Apparatus II; paddle, 75 rpm, 600 mL of 0.025% Tween 20 in water) as an interim specification. With respect to the proposed paddle speed, the Division of Biopharmaceutics felt that 50 rpm would be a more appropriate speed, than 75 rpm.

RECOMMENDATION:

Based upon the review of the dissolution data submitted in the supplement to NDA 19-697 filed on May 5, 1994 for ORTHO TRI-CYCLEN® Tablets, the Division of Biopharmaceutics believes that the comparative dissolution results are appropriate, however, the recommendation given for NDA 19-697 submitted on August 23, 1994 also applies to this submission. Therefore, this submission is acceptable with the understanding that the newly proposed dissolution method is accepted on an interim basis. As was indicated for the supplement to NDA 19-697 that was submitted on August 23, 1994, before a final dissolution method and specification are accepted, the Division of Biopharmaceutics would like to see 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 50 and 75 rpm and **ii)** at 15 and 20 minutes sampling times.

Please convey the Recommendation as appropriate to the sponsor.

NOTE: Attachment I is been retained in the Division of Biopharmaceutics and can be obtained upon request.

Angelica Dorantes

Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch

RD initialed by John Hunt. JPH 12/13/94
RD initialed by John Hunt. 12/14/94

cc: NDA 19-697, HFD-510, HFD-427 (Dorantes), Drug, Chron, and HFD-19 (FOI)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 13 1994

NDA No. 19-697

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

Attention: Isabel B. Drezewiecki

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-004

Date of Supplement: May.5,1994

Date of Receipt: May 10, 1994

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,

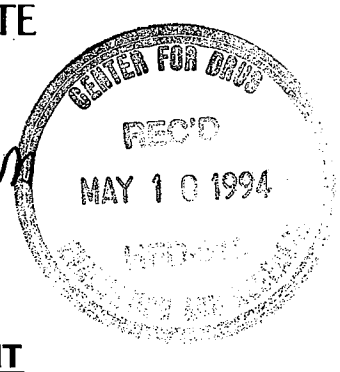
Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research

ORIGINAL

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

NDA NO. 19697 REF. NO. 004
NDA SUPPL FOR [redacted] SCM

MAY 05 1994



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

SUPPLEMENT

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

Dear Sir/Madam:

Reference is made to our approved New Drug Application 19-697 for ORTHO TRI-CYCLEN® Tablets. In accordance with the provisions of 21 CFR 314.70(b)(2)(vi), we are submitting a supplemental application to provide for Johnson & Johnson Pharmco (P.R.) Inc., Manati, Puerto Rico, as an additional site for the packaging of ORTHO TRI-CYCLEN Tablets. This facility is currently approved for the manufacture and testing of ORTHO TRI-CYCLEN Tablets. The packaging process and equipment train employed by Johnson & Johnson Pharmco (P.R.) Inc., are equivalent to those of our current approved packaging site, Ortho Pharmaceutical Corporation in Raritan, New Jersey.

In support of this supplement, we have appended Chemistry, Manufacturing and Control Information which includes 6-month stability data on three batches each of the 180 µg norgestimate/35 µg EE, and 215 µg norgestimate/35 µg EE strength tablets. The 250 µg norgestimate/35 µg EE strength tablets which represent the "high" dose of the triphasic regimen are currently packaged at Johnson & Johnson Pharmco (P.R.) Inc. as our monophasic product ORTHO-CYCLEN.

Please be advised that Johnson & Johnson Pharmco (P.R.) Inc. was previously named Ortho Pharmaceuticals, Inc. The renaming of this facility was reported to the Agency on April 21, 1994. The location, functions, size and staff of this facility remain unchanged. Because the supporting documentation contained in this supplement was generated and completed prior to this recent name change, the former name Ortho Pharmaceuticals, Inc. has been used throughout for consistency.

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER AP ☐ NAI

LA JOLLA RARITAN SPRING HOUSE TORONTO ZURICH

INITIALS 12-22-94 DATE

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

If you have any questions, please contact me at 908 704-4547.

Sincerely,

The R. W. Johnson Pharmaceutical
Research Institute

I.B. Drzewiecki

Isabel B. Drzewiecki
Senior Director
Regulatory Affairs

\srlb
Enclosures

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