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

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)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-009

APPROVAL LETTER

ORIGINAL

NDA 19-697/S-009

FEB - 7 1996

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 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[ ]%.

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

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

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)

ORIGINAL

FEB - 2 1996

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-510

2. NDA Number
19-697

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-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: $C_{23}H_{31}NO_3$ MW: 369.50
Ethinyl Estradiol: 19-nor-17-α-pregna-1,3,5-(10)-trien-20-yne-3,17-diol
Empirical Formula: [ ] 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

Redacted 2 page(s)

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

NDA SUPPL AMENDMENT SCS-009 BC ORIGINAL

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. mjr 2/5/96

FEB 0 1 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

CENTER FOR DRUG REC'D FEB 0 2 1996 HFD-510 EVALUATION AND RESEARCH

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 Jhong 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%.

n:\orthotri\ltr\dp0326.mp

FEB 0 1 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 Panasewicz
Manager
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☑ LETTER ☐ N.A.I.

CSO INITIALS 6/7/96 DATE

Enclosures

DP:mp

n:\orthotri\ltr\dp0326.mp

ORIGINAL
NDA SUPPL AMENDMENT
#5-009-5C

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

DEC 22 1995

CENTER FOR DRUG
HFD-510
DEC 26 1995
BRANCH

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 .

[redacted]

We have included in Item I a summary of data by batch number, supplier, test station and % [redacted]. 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:

☒ LET[illegible] ☐ N.A.I.

CSO [illegible] 2/7/96 DATE

Very truly yours,

The R. W. Johnson
Pharmaceutical Research Institute

Donna Panasewicz
Manager
Regulatory Affairs

n:\orthotri\ltr\dp3425.lg

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

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 Cont4rol Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

Supplement - Expedited 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 take 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 ≤[ ]%.
- 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 /% over 36 months. The total impurity stability specification for the NRG 0.250 mg/EE 0.35 mg. will remain at ≤[]%. Additionally, the release specification for total impurities for all three dosage strengths will remain at ≤ []%.

Based upon the results of our investigation and the fact that the original NDA specification of /% 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

CSO ACTION:

☐ LETTER ☐ N.A.L.

CSO INITIALS 7/7/96 DATE

Very truly yours,

The R.W. Johnson
Pharmaceutical Research Institute

Donna Panasewicz

Donna Panasewicz
Manager
Regulatory Affairs

DP/lg
Enclosures
n:\orthotri\ltr\dp2645.lg

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