CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-697/S-002

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: 02/16/1995

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-002

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Non-Approval Letter	**X**
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:

19-697/S-002

APPROVAL LETTER

NDA 19-653/S-009
NDA 19-697/S-002

FEB 16 1995

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

Dear Ms. Drzewiecki:

Please refer to your July 26, 1993, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

Ortho-Cyclen (NDA 19-653) and
Ortho-TriCyclen (NDA 19-697)
(norgestimate and ethinyl estradiol) Tablets.

We also refer to your amendments dated August 23, 1994, submitted in response to our deficiency letter of May 6, 1994.

The supplements provide for a new non-alcoholic based dissolution method (DM 91-020) with a tentative dissolution specification of Q=80% at 20 minutes for both norgestimate and ethinyl estradiol.

We have completed the review of these supplemental applications and they are approved. A final dissolution specification should be established in new supplements after additional data are accrued for one year using the new dissolution method DM 91-020 (USP Apparatus II, 600 ml of 0.025% Tween 20 in water) at 50 rpm and 75 rpm, and at 15 and 20 minute sampling times. It is understood that the dissolution method DM 91-020, with tentative specification of Q=80% at 20 minutes for both norgestimate and ethinyl estradiol, will now be included as a requirement for both product release and stability of these tablets.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Dr. Lisa Stockbridge at 301-443-3520.

Sincerely yours,

2/15/95

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

cc:
Original NDAs (2)
DISTRICT OFFICE
HFD-510 (2)
HFD-510\SSobel\YChiu\MRhee
HFD-426\ADorantes\JHunt
HFD-510\LStockbridge/2.14.95\19653bap.s09 2-15-95

Concurrences: MRhee/YChiu/EGalliers 02.15.95

SUPPLEMENTS APPROVED (AP)

NDA 19-653/S-009
NDA 19-697/S-002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-002

NON-APPROVAL LETTER

NDA 19-653/S-009
NDA 19-697/S-002

MAY - 6 1994

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

Dear Ms. Drzewieki:

Please refer to your July 26, 1993, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

Ortho-Cyclen (NDA 19-653) and
Ortho-TriCyclen (NDA 19-697)
(norgestimate and ethinyl estradiol) Tablets

The supplements provide for a new non-alcoholic based dissolution method (DM 91-020).

We have completed our review and find the information presented is inadequate and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. To support the rationale for using the dissolution medium, that is somewhat different than the more classical media, plus the selected paddle rotation speed of 75 rpm, the following information must be provided:

   a) pH solubility data for norgestimate and ethinyl estradiol

   b) sink condition information at 37°C for various media

   c) tablet dissolution profiles (including raw data) in media that provide adequate sink conditions with appropriate sample times to characterize a profile (e.g., distilled water, simulated gastric fluid without enzymes, simulated intestinal fluid without enzymes, different buffers, etc.)

   d) raw data and profiles at different paddle rotation speeds (50 and 75 rpm) in the different dissolution media where sink conditions exist.

2. Individual and mean dissolution data and profiles at 5,10, 15, 20 and 30 minutes for three production batches (12 tablets of each strength; 0.180 mg NGS/0.035 mg EE, 0.215 mg NGS/0.035 mg EE, and 0.250 NGS/0.035 mg EE) should be provided.

3. If it is determined that the dissolution method DM91-020 is acceptable (i.e., dissolution medium is justified, etc.) then the proposed dissolution specification (Q=80% at 30 minutes) is probably not going to be acceptable because a 30 minute dissolution test is not able to discern minor differences in tablet hardness or [ ]. An earlier test time (e.g., 10 or 15 minutes) would be warranted.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact Dr. Lisa L. Stockbridge at (301) 443-3520.

Sincerely yours,

5-6-94

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

cc:
Arch NDAs (2)
HFD-510 (2)
HFC-130/JAllen
HFD-510/YChiu/MRhee/RBennett
HFD-427/JHunt/ADorantes
HFD-80
drafted/LStockbridge/4.21.94\N19653A.SNA
revised/JHunt/4.28.94/ft/LLS/4.28.94 5-6-94

Concurrences:MRhee 4.21/YChiu/ADorantes/4.25/JHunt 4.28/EGalliers 5.3.94

SUPPLEMENTS NOT APPROVABLE

NDA 19-653/S-009
NDA 19-697/S-002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-510

MAR 2 3 1994

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

ORIGINAL

4. Supplement
S-002
7-26-93

5. Name of Drug
Ortho-TriCyclen

6. Nonproprietary Name
Norgestimate/EE tablets

7. Supplement Provides For
A new dissolution method.

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 dissolution method (DM 91-020), which is to fulfill their commitment to develop nonalcoholic based dissolution method. This new method utilizes 600ml of dissolution medium containing 0.025% (w/v) polyoxyethylene sorbitan monolaurate. Apparatus is USP Apparatus II (paddles) with 75% rpm positioned [redacted]mm from the inside bottom of the vessel.

16. Conclusion and Recommendation
The proposed dissolution method is acceptable, however, the dissolution specification (Q=80% at 30 minutes) is not acceptable based on Biopharm's recommendation. Issue a not-approvable letter with information requests described in the Biopharm's Review.

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

Reviewer's Signature

Date
3-22-94

Distribution Original Jacket Reviewer Division File
R/D initialed by
SL.178

3/23/94

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #1

19-697/S-002

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-510

2. NDA Number
19-697

DEC 21 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-002
7-26-93
Chem Rev #2

ORIGINAL

5. Name of Drug
Ortho-TriCyclen

6. Nonproprietary Name
Norgestimate/EE tablets

7. Supplement Provides For
A new dissolution method.

8. Amendment
8-23-94

9. Pharmacological Category
Oral contraceptive

10. How Dispensed
RX

11. Related
IND/NDA/DMF
NDA 19-653/S009

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
The original supplement was not approved because of deficiencies found by the Division of Biopharmaceutics. This amendment was submitted in response to the not-approvable letter (5-6-94) and it was sent for consult review to the Division of Biopharmaceutics. According to Dr. Angelica Dorantes' review, the proposed interim dissolution specification, Q=80% at 20 min, under the condition (USP apparatus II, paddle 75rpm, 600ml of 0.025% Tween 20 in water) is acceptable. However, the Biopharm expressed their desire to see additional data accrued for one year using the proposed method at 50rpm and 75rpm, and at 15 and 20 minutes.

16. Conclusion and Recommendation
This supplement is now approvable. Issue an approval letter with recommendation from the Division of Biopharmaceutics (see Dr. Dorates Review, 12-14-94).

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

Reviewer's Signature

Date
12-21-94

Distribution **Original Jacket** **Reviewer** **Division File**
R/D initialed by
SL-1.178

12/21/94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

See revisions by John Hewitt, dated 4-28-94, on draft letter (attached)

MAR 17 1994

4-28-94

NDA 19-697

SUBMISSION DATE: July 26, 1993

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: Supplement to provide Dissolution Data **Code: 3 S**

SYNOPSIS:

The sponsor is submitting a supplement to NDA 19-697 for ORTHO TRI-CYCLEN® Tablets. Reference is made to FDA's approval letter dated July 3, 1992 for ORTHO TRI-CYCLEN® Tablets and to a June 29, 1992 submission, in which the sponsor comitted to submit an *in vitro* non-alcoholic-based dissolution method to replace the sponsor's current hydroalcoholic method.

Accordingly, in this supplement the sponsor is submitting a dissolution method (DM 91-020) for norgestimate/ethinyl estradiol tablets employing a method using 0.025% (w/w) polyoxyetylene sorbitan monolaurate (Tween 20) in water as the dissolution medium. The sponsor's proposed dissolution specification is Q=80% at 30 minutes for norgestimate and ethinyl estradiol. In support of this supplement the sponsor has included the following:

1. Proposed dissolution method: DM 91-020 (see Attachment I).

2. Validation reports QA 4057, QA 4058, and QA 4059 of the analytical method used in the dissolution studies for 0.180 mg NGS/0.035 mg EE, 0.215 mg NGS/0.035 mg EE, and 0.250 mg NGS/0.035 mg EE tablets, respectively (see Attachment II).

3. Information on discrimination studies conducted for the proposed dissolution method (see Attachment III).

RECOMMENDATION:

Based upon the review of the dissolution data submitted in the supplement to NDA 19-697 filed on July 26, 1993 for ORTHO TRI-CYCLEN® Tablets, the Division of Biopharmaceutics feels that the proposed dissolution method and Reports QA 4057, QA 4058, and QA 4059 for the analytical performance (linearity, recovery, precision, and ruggednes) of the assay used for the determination of the dissolution samples, are appropriate. However, additional dissolution information as outlined under Comments 1 and 2 below should to be provided for review before the proposed dissolution method is accepted.

1. To support the rational for using the dissolution medium and its volume plus the selected paddle rotation speed of 75 rpm for the proposed dissolution method DM 91-02 the following information should be provided:

a) pH solubility data for norgestimate and ethinyl estradiol.

b) Sink condition information at 37°C for various media.

c) Tablet dissolution profiles (including raw data) in media that provide adequate sink conditions with appropriate sampling times to characterize a profile (i.e., distilled water, simulated gastric fluid [without enzymes], simulated intestinal fluid [without enzymes], different buffers, etc.).

d) Raw data and profiles at different paddle rotation speeds (50 rpm and 75 rpm) in the different dissolution media.

2. For method DM 91-020 provided should be individual and mean dissolution data and profiles at 5, 10, **15**, 20, and 30 minutes for three production batches (12 tablets of each strength; 0.180 mg NGS/0.035 mg EE, 0.215 mg NGS/0.035 mg EE, and 0.250 mg NGS/0.035 mg EE).

3. Regarding the sponsor's proposed specification of Q=80% at 30 minutes for NGS/EE, the Division of Biopharmaceutics feels that the selected specification is not appropriate because, a 30 minutes the dissolution test is not able to discern minor differences in tablet hardness or lubrication (see Figures 1 to 5 of discrimination studies in Attachment III). Once the requested additional dissolution information is provided, and if it is ultimately determined that the proposed dissolution method DM 91-020 is acceptable, then the proposed specification of Q=80% in 30 minutes would probably need to be changed to Q=80% at either 10 or 15 minutes in order to have a dissolution specification that would adequately detect the effect of minor differences in formulation or production changes.

Please convey the Recommendation and Comments 1 and 2 as appropriate to the sponsor.

NOTE: Attachment I to III are 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 3/16/94

RD initialed by John Hunt. J. Hunt 3/17/94

cc: NDA 19-697, HFD-510, HFD-426 (Dorantes), HFD-426 (Fleischer), Drug, Chron, and HFD-19 (FOI)

DEC 14

NDA 19-653 /S-009
ORTHO-CYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

NDA 19-697 /S-002
ORTHO-TRICYCLEN® Tablets
Norgestimate/Ethinyl Estradiol

SUBMISSION DATE: August 23, 1994

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

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplemental Amendments - Dissolution Data **Code: 3 S**

SYNOPSIS:

On August 23, 1994 the sponsor submitted an amendment to supplement No. 9 under NDA 19-653 for ORTHO-CYCLEN® Tablets and an amendment to supplement No. 2 under NDA 19-697 for ORTHO-TRICYCLEN® Tablets. In these supplemental amendments reference is made to a previous supplemental applications 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 applications (see Attachment I). In these August 23, 1994 supplemental amendments to NDAs 19-653 and 19-697, the sponsor has included their responses to the Biopharm deficiencies outlined in the May 6, 1994 Agency's letter (see Attachment II).

Related to the dissolution specifications for method DM 91-020, it should be noted that R.W. Johnson Pharmaceutical Research Institute (PRI) acknowledges that the proposed FDA specification of Q=80% at 15 minutes can be supported with the currently available data. However, they indicated that the production scale dissolution data available using method DM 91-020 are limited, and it would be premature to adopt the proposed FDA's dissolution specification at this time. Therefore, upon approval of these supplemental amendments PRI committed itself to provide additional dissolution data (i.e., dissolution data at 15 and 20 minutes for all production size batches of the three NGS/EE tablet strengths, including both release and stability data). At the end of one year, the data accrued will be evaluated and a final dissolution specification will be proposed. A supplemental application(s) will then be filed with the FDA.

RECOMMENDATION:

Based upon the review of the dissolution data submitted in the supplemental amendments to NDA 19-653 for ORTHO-CYCLEN® Tablets and NDA 19-697 for ORTHO-TRICYCLEN® Tablets which were filed on August 23, 1994, the Division of Biopharmaceutics believes that the sponsor responses to Deficiencies 1 (a, b, and c) and 2 listed in the Agency's letter dated May 6, 1994 are adequate, and they are acceptable. With respect to Deficiency No. 1d, the results indicate that the 50 rpm paddle speed did not significantly decrease the dissolution of either norgestimate or ethinyl estradiol. Therefore, the Division of Biopharmaceutics believes that a paddle speed of 50 rpm is more appropriate than 75 rpm. Regarding Deficiency No. 3, 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), is acceptable on an the interim basis.

With respect to the sponsor's commitment to provide additional data upon approval of these supplemental amendments, the Division of Biopharmaceutics feels that this is a reasonable approach. However, before a final dissolution method and specification are accepted, the Division of Biopharmaceutics 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 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 and II are 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 11/6/94
FT initialed by John Hunt. J. Hunt 12/14/94

cc: NDA 19-653 & 19-697, HFD-510, HFD-427 (M. Chen, Dorantes), Drug, Chron, and HFD-19 (FOI)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-697/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date 8-5-93

NDA No. 19-697

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

Attn: Thomas Koestler, Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ORTHO-TriCyclen Tablets (norgestimate & ethinyl Estradiol)

NDA Number: 19-697

Supplement Number: S-002

Date of Supplement: July 26, 1993

Date of Receipt: July 28, 1993

All communications concerning this NDA should be addressed as follows:

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

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

I talked to Sandy Cuthbertson @ PRI and confirmed that this is a new supplement (prior approval) for a new dissolution method & specs for both 19-695 & 19-697. I said that a 356h should have been attached, but NOT to send one in for this supplement unless they needed to amend it. SMC 8/4/93

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

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

NDA NO. 19697 REF. NO. 002
NDA SUPPL FOR SCS

JUL 2 6 1993

~~Pre-approval~~ Supplement

Solomon Sobel, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Review II, HFD #510
Attention: Document Control Room #14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 19-697
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)
Cross refer to:
NDA 19-653
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Dear Dr. Sobel:

Reference is made to your July 3, 1992 approval letter for ORTHO TRI-CYCLEN and to our June 29, 1992 submission in which we committed to submit an in-vitro non-alcoholic-based dissolution method to replace our current hydroalcoholic method. At this time we are submitting a dissolution method (DM 91-020) for norgestimate/ethinyl estradiol tablets employing a method using 0.025% (w/v) polyoxyethylene sorbitan monolaurate (Tween 20) in water as the dissolution medium. Our proposed dissolution specification is Q=80% at 30 minutes for norgestimate and ethinyl estradiol.

In support of this supplement, we have appended the following:

- Our proposed dissolution method (DM 91-020).
- Reports QA 4057, QA 4058, and QA 4059. These reports detail the validation of the dissolution method for 0.180 mg norgestimate/0.035 mg ethinyl estradiol, 0.215 mg norgestimate/0.035 mg ethinyl estradiol and 0.250 mg norgestimate/0.035 mg ethinyl estradiol tablets, respectively.
- Information on discrimination studies we have conducted for the proposed dissolution method. ORTHO-CYCLEN and CILEST Tablets of various hardnesses and those manufactured from [redacted] mg magnesium stearate, which is our

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER 5-6-94 ☐ N.A.I.
CSO INITIALS 5-6-94 DATE

JUL 2 6 1993

approved formulation) were used to test the method's ability to discern minor differences in tablets. The CILEST Tablets were manufactured by our affiliate, Cilag Ltd. in England, and the ORTHO-CYCLEN Tablets were manufactured in Raritan. The formulations and specifications for ORTHO-CYCLEN and CILEST Tablets are the same. Results of the studies demonstrate the proposed dissolution method can discern minor differences in tablets such as hardness and [redacted]. Therefore, we would consider this dissolution method to be discriminating.

Should you have any questions, please contact me directly at (908) 704-4038.

Sincerely,

Thomas P. Koestler, Ph.D.
Senior Director
Regulatory Affairs

SR\lb

oc\sobel.624

ORIGINAL

noted 5/25/94 RLB

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

MAY 20 1994

noted MM 5/25/94

Solomon Sobel, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Review II, HFD #510
Attention: Document Control Room #14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 19-653 (S-009)
ORTHO-CYCLEN® Tablets

NDA 19-697 (S-002)
ORTHO TRI-CYCLEN® Tablets

Noted, KRahija 5/25/94

Dear Dr. Sobel:

Reference is made to our supplemental new drug applications dated July 26, 1993, which provide for a new non-alcoholic based dissolution method (DM 91-020), and to your not-approvable letter (copy attached) dated May 6, 1994 and received on May 19, 1994. We are currently compiling the information requested and plan to respond to the noted deficiencies as soon as possible.

In accordance with 21 CFR 314.120, we wish to notify you of our intent to file an amendment to each of the supplemental NDAs referred to above in support of approval of these applications.

Should you have any questions, please contact me directly at (908) 704-4038.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I.
CSO INITIALS 5-26-94 DATE

Very truly yours,

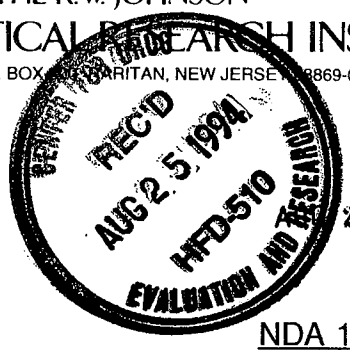
I.B. Drzewiecki

Isabel B. Drzewiecki
Senior Director
Regulatory Affairs

\srlb
Attachment

\ortho_cy\letters\sobel.m20

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



ORIGINAL

AUG 23 1994

Solomon Sobel, M.D.
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

NDA 19-697 (S-002) ✓
ORTHO TRI-CYCLEN® Tablets

Cross refer to:
NDA 19-653 (S-009)
ORTHO-CYCLEN® Tablets

Dear Dr. Sobel:

Reference is made to the above supplemental new drug applications dated July 26, 1993, which provide for a new non-alcoholic based dissolution method (DM 91-020). Reference is also made to your May 6, 1994, not-approvable letter (copy attached) listing the deficiencies in these supplemental applications.

At this time, we are submitting our responses to the deficiencies outlined in your letter. We trust that these responses satisfactorily address your concerns.

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 amendment to our pending supplemental applications.

Should you have any questions, please contact me directly at (908) 704-4547.

Very truly yours,

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER AP
☐ N.A.P.
12-15-94
DATE
CSO INITIALS

Isabel B. Drzewiecki
Senior Director
Regulatory Affairs

\srlb
Attachment

Please see Biopharm's Review (12-14-94) and issue an "Approval" letter with their recommendation
MJR 12/19/94