CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-690

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: April 19, 2005

To: NDA 21-690, N-000, ORTHO TRI-CYCLEN® Tablets

From: Yvonne Yang, Ph.D.
Chemist Reviewer, HFD-510

Subject: Overall Compliance Recommendation

NDA 21-690 ORTHO TRI-CYCLEN® Tablets was submitted Sept-24-2003. An Approvable letter dated Mar-23-2004 was issued by the Agency for (1) Clinical (requirement for the submission and review of the final results from the 12-month study, CAPSS-169), and (2) CMC (overall **WITHOLD** recommendation from Office of Compliance for one of the manufacturing facilities). A complete response was submitted on Nov-18-2004.

An overall **ACCEPTABLE** cGMP status has been granted by the Office of Compliance on Dec-21-2004 (see attached EER report for details).

All chemistry, manufacturing and controls sections of NDA 21-690 have been reviewed and found sufficient to support the approval of this application (see CMC review #1 dated Mar-12-2004 and this memo dated Apr-19-2005 for details).

From the standpoint of chemistry, manufacturing and controls, this NDA can be approved pending a satisfactory review of the revised labeling.

Cc: NDA # 21-690, N-000
HFD-510/Division file
HFD-510/Y Yang
HFD-510/M Gautam-Basak
HFD-510/P Madara

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21690/000 Sponsor: ORTHO MCNEIL

Org Code : 510 300

Priority : 6P RARITAN, NJ 08869

Stamp Date : 25-SEP-2003 Brand Name : ORTHO TRI-CYCLEN(ETHINYL

PDUFA Date : 19-MAY-2005 ESTRADIOL/NORGE

Action Goal : Estab. Name:

District Goal: 25-JAN-2004 Generic Name: ETHINYL

ESTRADIOL/NORGESTIMATE

TABLETS

Dosage Form: (TABLET)

Strength : 0/0,180/35,215/35,250/3

FDA Contacts: P. MADARA Project Manager (HFD-510) 301-827-6416

Y. YANG Review Chemist (HFD-510) 301-827-6371

M. GAUTAM HASAK Team Leader (HFD-510) 301-827-9084

Overall Recommendation: ACCEPTABLE on 21-DEC-2004by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 11-MAR-2004by C. CRUZ (HFD-323) 301-827-9013

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-NOV-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-NOV-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : [redacted]

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2211100 FEI : 2211100
ORTHO PHARMACEUTICAL CORP
1000 RTE 202
RARITAN, NJ 08869

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-DEC-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2650078 FEI : 2650078
ORTHO PHARMACEUTICALS INC
BO CAMPO ALEGRE RD NO 2KM 45.6
MANATI, PR 00674

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-DEC-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yvonne Yang
4/21/05 02:47:36 PM
CHEMIST

Mamta Gautam-Basak
4/21/05 02:53:16 PM
CHEMIST
Concur

NDA 21-690

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

Ortho-McNeil Pharmaceutical, Inc.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
(Authorized U.S. Agent)

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-690

2. REVIEW #: #1

3. REVIEW DATE: Mar-12-2004

4. REVIEWER: Yvonne Yang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Sept-23-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Ortho-McNeil Pharmaceutical, Inc.
U. S. Representative:	Johnson & Johnson Pharmaceutical Research Development, L.L.C.
Address of U. S. Representative:	920 Route 202 South P.O. Box 300 Raritan, NJ 08869-0602
Telephone:	(908) 704-5067

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	ORTHO TRI-CYCLEN®
b) Non-Proprietary Name (USAN):	Norgestimate/ethinyl estradiol (NGM/EE)
c) Code Name/# (ONDC only):	RWJ 10131
d) Chem. Type/Submission Priority (ONDC only):	
• Chem. Type:	6
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

This NDA is submitted to fulfill the Agency's requirements of the Written Request for Pediatric Studies dated Nov-12-2002.

10. PHARMACOL. CATEGORY: HRT/Osteoporosis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Norgestimate/ethinyl estradiol (NGM/EE)
180 µg/35 µg
215 µg/35 µg
250 µg/35 µg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx _____ OTC

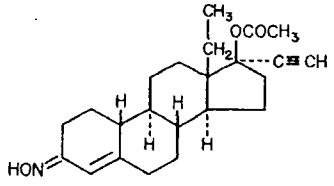
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

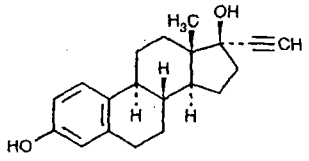
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norgestimate:
(a) 18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-
(b) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester)
$C_{23}H_{31}NO_3$ MW = 369.50



Ethinyl estradiol:
(a) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-
(b) 19-Nor-17α-pregna-1,3,5(10) trien-20-yne-3,17-diol
$C_{20}H_{24}O_2$ MW = 296.40



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	Oct-18-1999	Reviewed by Ali Al-Hakim
	II			3	Adequate	May-23-2001	Reviewed by Jila Boal
	II			3	Adequate	Dec-09-2002	Reviewed by Amit Mitra
	III			3	Adequate	Mar-06-1998	Reviewed by Ali Al-Hakim
	III			3	Adequate	May-30-2003	Reviewed by Lorenzo Rocca
	III			3	Adequate	Jul-30-2003	Reviewed by Chong-Ho Kim

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	11,391	ORTHO TRI-CYCLEN® Tablets (HFD-580)
NDA	19-697	ORTHO TRI-CYCLEN® Tablets (HFD-580)
NDA	19-653	ORTHO CYCLEN® Tablets (HFD-580)
IND	61,239	ORTHO TRI-CYCLEN® Tablets (HFD-510) Pediatric studies

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Withhold	Mar-11-2004	Yvonne Yang
EA	Categorical exclusion granted	Mar-12-2004	Yvonne Yang
Pharm/Tox	N/A		
Biopharm	Unacceptable due to the sparsity of the data	Mar-08-2004	Steven Johnson
Biometrics	Final conclusion should be made after review of Cycle 13/Final Visit data	Feb-25-2004	Cynthia Liu
LNC	N/A		Yvonne Yang
Methods Validation	N/A		Yvonne Yang
Microbiology	N/A		Yvonne Yang
ODS/DMETS	N/A		

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 21-690

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of chemistry, manufacturing and controls, NDA 21-690 is approvable pending resolution of all issues related to a **Withhold** recommendation from the Office of Compliance on Mar-11-2004.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

No CMC or nonclinical development information was submitted in this NDA. All CMC information remains as approved under NDAs 19-697 and 19-653. A brief summary is included for administrative purposes.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

ORTHO TRI-CYCLEN® Tablets is an approved triphasic combination oral contraceptive containing the progestational compound norgestimate (0.180-0.250 mg) and the estrogenic compound ethinyl estradiol (0.035 mg). ORTHO TRI-CYCLEN® is currently indicated "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, ≥ 15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications". Components and compositions of ORTHO TRI-CYCLEN® Tablets including inactive ingredients are summarized in the table on page 8.

ORTHO TRI-CYCLEN® is available in a DIALPAK® Tablet Dispenser (NDC 0062-1903-15) containing 28 tablets (7 unscored white tablets with "Ortho" and "180" debossed on each side; 7 unscored light blue tablets with "Ortho" and "215" debossed on each side; 7 unscored blue tablets with "Ortho" and "250" debossed on each side, and 7 green tablets containing inert ingredients). ORTHO TRI-CYCLEN® is also available as Refills (NDC

0062-1903-23). Each package of ORTHO TRI-CYCLEN® is intended to deliver a 28-day regimen.

The current expiry for ORTHO TRI-CYCLEN® is 36 months, stored at 25 °C (77 °F) with excursions permitted to 15°-30°C (59°-86°F) (NDA 19-697).

Name used in Patient Labeling	No. of Tablets	Color of Tablet	NGM (mg)	EE (mg)	To-Be-Administered	Inactive Ingredients
Active pills (with hormones)	7	White	0.180	0.035	Days 1-7	Lactose, magnesium stearate, and pregelatinized starch
	7	Light blue	0.215	0.035	Days 8-14	FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch
	7	Blue	0.250	0.035	Days 15-21	
Reminder pills (without hormones)	7	Green	0	0	Days 22-28	D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch

Drug Substance:

ORTHO TRI-CYCLEN® contains two Active Pharmaceutical Ingredients, norgestimate (NGM) and ethinyl estradiol, USP (EE). Norgestimate and ethinyl estradiol are synthetic steroid hormones possessing progestational and estrogenic properties, respectively.

Norgestimate is a white to pale yellow (off-white) fine granular powder. It is insoluble in water, sparingly soluble in acetonitrile, and freely to very soluble in methlyene chloride. Norgestimate is a mixture of (E)- and (Z)-isomers having a ratio of (E)- to (Z)-isomer between 1.27 and 1.78. Relevant information regarding chemistry, manufacturing, and controls of norgestimate is provided in DMF [redacted] and DMF [redacted] and found adequate to support the original NDA 19-697 (in HFD-580) and the current NDA 21-690 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

Ethinyl estradiol is a white to creamy white, odorless, crystalline powder. It is practically insoluble in water; soluble in alcohol, ether, acetone, dioxane, chloroform, vegetable oils, and in solutions of fixed alkali hydroxides. Ethinyl estradiol, USP is manufactured in accordance with the specifications and test methods described in the current USP monograph. Ethinyl estradiol is a synthetic steroid with high oral estrogenic potency.

B. Description of How the Drug Product is Intended to be Used

ORTHO TRI-CYCLEN® is available in a DIALPAK® Tablet Dispenser (NDC 0062-1903-15) containing 28 tablets (7 unscored white tablets with

"Ortho" and "180" debossed on each side; 7 unscored light blue tablets with "Ortho" and "215" debossed on each side; 7 unscored blue tablets with "Ortho" and "250" debossed on each side, and 7 green tablets containing inert ingredients). ORTHO TRI-CYCLEN® is also available as Refills (NDC 0062-1903-23). Each package of ORTHO TRI-CYCLEN® is intended to deliver a 28-day regimen.

The patient is instructed to take one ORTHO TRI-CYCLEN® tablet every day at the same time for best results. The patient may choose to start with either the **Sunday Start** or the **Day 1 Start** regimen. With the **Sunday Start** regimen, the patient is instructed to take the first white tablet of the pack on the Sunday after the period starts, even if the patient is still bleeding. A back-up birth control method is recommended for patients using the Sunday Start regimen during the first week. With the **Day 1 Start** regimen, the patient is instructed to take the first white tablet of the pack during the first 24 hours of her period. A back-up birth control method is not necessary for patients using the Day 1 Start regimen. For both regimens, the patient is instructed to take one white tablet every day for days 1-7, one light blue tablet every day for days 8-14, one blue tablet every day for days 9-21, and one green tablet every day for days 22-28. The patient is instructed to take one tablet every day at the same time until the whole pack is empty, and to start with the next pack immediately on the day after the last reminder (green) pill. Specific and detailed instructions are included in the Patient Labeling for patients who missed one or more tablets, under various situations, for best corrective measures.

C. Basis for Approvability or Not-Approval Recommendation

ORTHO TRI-CYCLEN® is an approved drug product (NDA 19-697) with no outstanding CMC issues. An overall recommendation of Withhold is issued from the Office of Compliance on Mar-11-2004. The application is **Approvable** from the CMC standpoint.

III. Administrative

A. Reviewer's Signature in DFS

B. Endorsement Block in DFS

C. CC Block in DFS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yvonne Yang
3/12/04 01:01:17 PM
CHEMIST

Mamta Gautam-Basak
3/12/04 01:06:16 PM
CHEMIST
Concur