

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-241

**CHEMISTRY REVIEW(S)**

**NDA # 21-241**

**ORTHO TRI-CYCLEN<sup>®</sup> LO**  
**(Norgestimate and Ethinyl estradiol) Tablets**

**The R. W. Johnson**  
**Pharmaceutical Research Institute**

**Jila H. Boal, Ph.D.**

**Division of Reproductive and Urologic Drug Products**  
**(HFD-580)**

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# CHEMISTRY REVIEW

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# Chemistry Review Data Sheet

1. NDA # 21-241
2. REVIEW # 3
3. REVIEW DATE: 10-August-2002
4. REVIEWER: Jila H. Boal, Ph. D.

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ON ORIGINAL**

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	25-AUG-2000
Amendment	08-NOV-2000
Amendment	22-JAN-2001
Amendment	27-MAR-2001
Amendment	11-MAY-2001
Amendment	07-JUN-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	03-AUG-2001
Amendment	25-JUN-2002
Amendment	16-AUG-2002

7. NAME & ADDRESS OF APPLICANT:

Name: The R. W. Johnson Pharmaceutical Research Institute

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

Address: 920 Route 202 South  
P.O. Box 300  
Raritan, New Jersey 08869-0602

Representative: NA

Telephone: NA

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ORTHO TRI-CYCLEN<sup>®</sup> Lo
- b) Non-Proprietary Name (USAN): Norgestimate / Ethinyl estradiol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Combination progestogen / estrogen.  
Oral contraceptive

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 180 µg norgestimate / 25 µg ethinyl estradiol  
215 µg norgestimate / 25 µg ethinyl estradiol  
250 µg norgestimate / 25 µg ethinyl estradiol

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X   Rx   \_\_\_  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

       SPOTS product – Form Completed

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

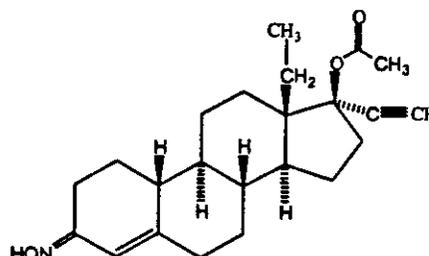
X  Not a SPOTS product

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

#### Norgestimate:

- 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 $\alpha$ )-(+)-
- (+)-13-Ethyl-17-hydroxy-18, 19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime acetate(ester)

**APPEARS THIS WAY  
ON ORIGINAL**



#### Molecular Formula:

$C_{23}H_{31}NO_3$

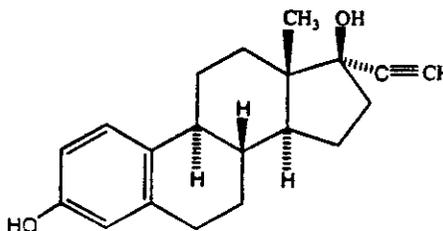
#### Molecular Weight:

#### CAS Registry Number:

35189-28-7

#### Ethinyl Estradiol:

- 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-
- 19-Nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol



#### Molecular Formula:

$C_{20}H_{24}O_2$

#### Molecular Weight:

#### CAS Registry Number:

57-63-6

**APPEARS THIS WAY  
ON ORIGINAL**

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Original NDA Chemistry Review 1.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS

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
NDA	19-653	ORTHO-CYCLEN®
NDA	19-697	ORTHO TRI-CYCLEN®
NDA	21-040	ORTHO-PREFEST™

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested		
EES	Satisfactory		See Chemistry Review # 1
Pharm/Tox	Satisfactory		See original NDA
Biopharm	Satisfactory		See original NDA

## CHEMISTRY REVIEW

### Executive Summary Section

Based on the drug product dissolution profile at release and stability the dissolution specification for norgestimate and ethinyl estradiol at release were revised to \_\_\_\_\_ at 20 minutes. The dissolution specification at stability were revised to the following: \_\_\_\_\_ ) at 20 minutes for ethinyl estradiol and \_\_\_\_\_ at 30 minutes for norgestimate. This decision is in concurrence with the Division of Clinical Pharmacology and Biopharmaceutics Reviewer Dr. Venkat Jarugula.

The applicant proposed a shelf life of \_\_\_\_\_ which could not be granted. Based on the real time data, an 18-month shelf life has been granted when stored at 25°C (77°F).

#### Drug Substances:

##### Norgestimate:

This compound is well-characterized and used in other approved drug products. There are \_\_\_\_\_ norgestimate drug substance, \_\_\_\_\_

\_\_\_\_\_ ). Both DMFs have been reviewed and determined to be acceptable to support this NDA. The quality attributes of norgestimate from both suppliers are comparable.

The norgestimate bulk drug substance is tested and qualified by the sponsor. Characterization of \_\_\_\_\_ norgestimate drug substance has been substantially studied by the applicant to support NDA 21-040.

RWJ has further characterized \_\_\_\_\_ norgestimate and has performed the following tests, the particle size distribution, thermal behavior ( \_\_\_\_\_ )

both suppliers ( \_\_\_\_\_ ) provide \_\_\_\_\_ ). Data do indicate that that norgestimate is a \_\_\_\_\_ An \_\_\_\_\_ that are the same and has also been generated.

Norgestimate process impurities include \_\_\_\_\_

\_\_\_\_\_ With the exception of \_\_\_\_\_ which is also a degradation product, process impurities will be controlled at the drug substance stage.

Release specifications for the norgestimate drug substance are, identification (IR, HPLC and optical rotation), physical description (visual exam), assay and purity by HPLC, \_\_\_\_\_ by HPLC, loss on drying, heavy metals, residue on ignition and particle size. The proposed specifications are adequate and are regulatory test methods with acceptance criteria that are identical to the approved NDA 21-040 for ORTHO-PREFEST™, approved NDA 19-653 for ORTHO-CYCLEN®, and approved NDA 19-697 for ORTHO TRI-CYCLEN®.

\_\_\_\_\_ Ethinyl Estradiol (USP and Ph. Eur. Grade Ethinyl Estradiol): Ethinyl estradiol is manufactured at \_\_\_\_\_

## CHEMISTRY REVIEW

### Executive Summary Section

This DMF was reviewed and found adequate to support this NDA.

Ethinyl estradiol USP is \_\_\_\_\_ and has been characterized at RWJPRI.

The specifications and methods for ethinyl estradiol are as follows: Identification (IR, UV, and TLC), physical description (visual exam), USP melting range, completeness of solution, USP specific rotation, particle size, residual solvents (GC), loss on Drying, assay and related substances by HPLC (the method is a modification of the USP method for assay of ethinyl estradiol). The USP method of ethinyl estradiol can not separate the two impurities, \_\_\_\_\_ whereas this method can.

The most significant impurity in drug substance lots is \_\_\_\_\_ which is also a degradation product and will be monitored in the drug product. The sponsor has submitted batch analysis for \_\_\_\_\_ representative lots of ethinyl estradiol to support the impurities and degradants acceptance criteria.

Stability of four lots of ethinyl estradiol, 48 months data for one lot, over 36 months for a second lot and over 24 months for the third and fourth lots of ethinyl estradiol are presented. Stability conditions are according to the ICH and tests include particle size, impurities, and the USP monograph tests for appearance, assay, loss on drying and specific rotation.

There are contract facilities that perform release and stability tests on the drug substances. They are listed in chemistry review # 1 and are in compliance with cGMP.

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

The 28 days regimen drug product will be packaged for commercial sale in blister ring with foil over wrap. After opening the foil wrap the user will place the blister ring in a DIALPAK<sup>®</sup> Tablet Dispenser for use. Each blister ring contains white NGM (180 µg) / EE (25 µg) tablets (Days 1 to 7), light blue NGM (215 µg) / EE (25 µg) tablets (Days 8 to 14), dark blue NGM (250 µg) / EE (25 µg) tablets (Days 15 to 21), and green placebo tablets (Days 22 to 28).

The product has an 18 month shelf-life under the recommended storage condition of: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F), and protected from light.

#### **C. Basis for Approvability or Not-Approval Recommendation**

This review finds the revisions described in the NDA and NDA amendments, and the final drug product label to be satisfactory. Therefore, there are no pending CMC issues in this NDA.

## CHEMISTRY REVIEW

### Executive Summary Section

This application was submitted on 25-August-2000 and deemed approvable on 25-June-2001. An Information Request Letter with regard to the CMC deficiencies in the original NDA submission was sent to the sponsor on 24-May-2001. The amendment of 07-June-2001 is the response to the deficiencies and all of the deficiencies have been satisfactorily addressed (see Chemistry review # 2 dated 20-June-2001). In addition, the sponsor has agreed to provide a copy of the revised drug product specification.

The amendment of 03-August-2001 contains the revised drug substance (ethinyl estradiol) and the drug product specifications. The revised drug product specifications submitted in the amendment of 03-August-2001 contained a typographic error with regard to dissolution specifications for norgestimate and ethinyl estradiol. The error was resolved and the corrected specifications and acceptance criteria for the drug product have been submitted via the amendment date 16-August-2002.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist Name / Date: Jila H. Boal, Ph.D. / 21-August-2002  
Chemistry Team Leader Name: David T. Lin, Ph. D.  
Project Manager Name / Date: Jennifer Mercier

#### C. CC Block

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

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Jila Boal  
8/21/02 05:09:28 PM  
CHEMIST

David T. Lin  
8/21/02 05:15:06 PM  
CHEMIST  
I concur.

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(A)

**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*11 pages*

(A)

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-241

**DATE REVIEWED:** June 20, 2001

**CHEMISTRY REVIEW #:** 2

**REVIEWER:** Jila H. Boal

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	August 25, 2000	August 29, 2000	September 1, 2000
Amendment	June 7, 2001	June 7, 2001	

**NAME & ADDRESS OF APPLICANT:** The R.W. Johnson Pharmaceutical Research Institute  
920 Route 202 South  
P.O. Box 300  
Raritan, New Jersey 08869-0602

**DRUG PRODUCT NAME**

Proprietary:

ORTHO TRI-CYCLEN<sup>®</sup>Lo

Nonproprietary/Established/USAN:

Norgestimate / Ethinyl estradiol

Code Name/#:

None

Chem.Type/Ther.Class:

3S

**PHARMACOL. CATEGORY/INDICATION:**

Prevention of pregnancy in women who elect to use oral contraceptive as a method of contraception

**DOSAGE FORM:**

Tablet

**STRENGTHS:**

180 µg norgestimate / 25 µg ethinyl estradiol  
215 µg norgestimate / 25 µg ethinyl estradiol  
250 µg norgestimate / 25 µg ethinyl estradiol

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:**

Rx  OTC

**SPECIAL PRODUCTS**

Yes  No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

**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, (17 $\alpha$ )-(+)-

b. (+)-13-Ethyl-17-hydroxy-18, 19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime acetate (ester)

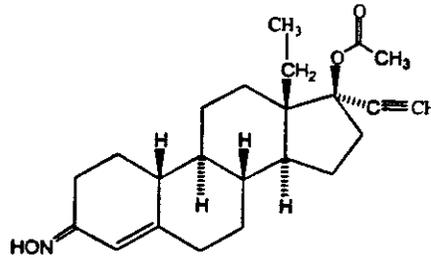
Molecular Formula: C<sub>23</sub>H<sub>31</sub>NO<sub>3</sub>

Molecular weight —

CAS Registry Number: 35189-28-7

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**APPEARS THIS WAY  
ON ORIGINAL**



Ethinyl Estradiol:

a. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-

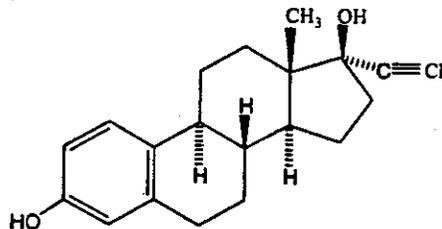
b. 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular Formula:  $C_{20}H_{24}O_2$

Molecular weight: \_\_\_\_\_

CAS Registry Number: 57-63-6

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**SUPPORTING DOCUMENTS:**

See Chem. Rev. #1.

**RELATED DOCUMENTS:**

See Chem. Rev. #1.

**PATENT STATUS:**

See Chem. Rev. #1.

**CONSULTS:**

See Chem. Rev. #1.

**REMARKS/COMMENTS:**

This review discusses the following issues.

1. The June 7, 2001 amendment, which is the sponsor's response to the FDA information request letter sent on May 24, 2001 pertaining to the chemistry review # 1. These are discussed below in this review # 2.
2. Component/Composition of the DIALPACK® Tablet Dispenser.

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ON ORIGINAL**

**CONCLUSIONS & RECOMMENDATIONS:**

From the chemistry, manufacturing and controls point of view this NDA can be approved.

cc:

Orig. NDA #21-241

HFD-580/Division File

HFD-580/JMercier

HFD-580/MRhee/Jboal

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---

Jila H. Boal, Ph.D.  
Review Chemist

R/D Init by:

filename: NDA 21-241 Review #2

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this page is the manifestation of the electronic signature.  
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/s/

-----  
Jila Boal  
6/21/01 03:32:54 PM  
CHEMIST

Moo-Jhong Rhee  
6/21/01 05:02:37 PM  
CHEMIST  
I concur

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14-JUN-2001

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Page 1 of 6

Application: NDA 21241/000  
Stamp: 25-AUG-2000  
Regulatory Due: 25-JUN-2001  
Applicant: R W JOHNSON  
920 RT 202 SOUTH  
RARITAN, NJ 088690602  
Priority: 3S  
Org Code: 580

Action Goal:  
District Goal: 26-APR-2001  
Brand Name: ORTHO TRI CYCLEN 25 (ETHINYL  
ESTRADIOL/NO  
Estab. Name:  
Generic Name: ETHINYL  
ESTRADIOL/NORGESTIMATE

Dosage Form: (TABLET)  
Strength: LOOK UP THE COMMENTS SE

Application Comment:

FDA Contacts: J. MERCIER (HFD-580) 301-827-4260, Project Manager  
J. BOAL (HFD-580) 301-827-4259, Review Chemist  
M. RHEE (HFD-580) 301-827-4237, Team Leader

Overall Recommendation: ACCEPTABLE on 14-JUN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062  
WITHHOLD on 04-JUN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No: AADA:  
Responsibilities:

Profile: CTL OAI Status: NONE  
Estab. Comment: (on 20-OCT-2000 by (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
OC RECOMMENDATION	23-OCT-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:  
Responsibilities:

Profile: CTL OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
SUBMITTED TO DO	23-OCT-2000	GMP			DAMBROGIOJ
DO RECOMMENDATION	25-OCT-2000			ACCEPTABLE BASED ON FILE REVIEW	LANDREWS
BASED ON PREVIOUS INSPECTION OF CTL PROFILE CLASS ON 6/19-23/00. PROFILE WAS ACCEPTABLE.					
OC RECOMMENDATION	25-OCT-2000			ACCEPTABLE	DAMBROGIOJ
SUBMITTED TO DO	01-MAY-2001	GMP		DISTRICT RECOMMENDATION	DAMBROGIOJ

ASSIGNED INSPECTION 02-MAY-2001 PS VSTOAKES  
INSPECTION PERFORMED 01-JUN-2001 04-MAY-2001 VSTOAKES  
CTL PROFILE ACCEPTABLE. PLEASE NOTE THAT THIS SITE DID NOT CONDUCT ANY  
TESTING IN SUPPORT OF NDA 21241.  
DO RECOMMENDATION 01-JUN-2001 ACCEPTABLE VSTOAKES  
INSPECTION

CTL PROFILE ACCEPTABLE BASED UPON 5/3/2001 INSPECTION. PLEASE NOTE THAT THIS  
LABORATORY DID NOT CONDUCT ANY TESTING IN SUPPORT OF NDA 21241.  
OC RECOMMENDATION 01-JUN-2001 ACCEPTABLE FERGUSONS  
DISTRICT RECOMMENDATION

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA:  
Responsibilities: \_\_\_\_\_  
Profile: CSN OAI Status: NONE  
Estab. Comment: \_\_\_\_\_ (on 20-OCT-  
2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
ASSIGNED INSPECTION	30-OCT-2000	GMP			EGASM
SUBMITTED TO OC	11-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			EGASM
ASSIGNED INSPECTION	16-JAN-2001	GMP			EGASM
INSPECTION SCHEDULED	22-FEB-2001		14-MAR-2001		IRIVERA
INSPECTION PERFORMED	16-MAR-2001		14-MAR-2001		EGASM
DO RECOMMENDATION	09-APR-2001			ACCEPTABLE INSPECTION	EGASM
BASED ON INVESTIGATOR'S COMMENTS, AND FIRM HISTORY					
OC RECOMMENDATION	09-APR-2001			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA:  
Responsibilities: \_\_\_\_\_  
Profile: CSN OAI Status: NONE  
Estab. Comment: \_\_\_\_\_ (on 20-OCT-2000 by J.  
BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
DO RECOMMENDATION	30-OCT-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 9/23/99					
OC RECOMMENDATION	30-OCT-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: \_\_\_\_\_

DMF No: 2364

Responsibilities:

Profile: CSN

Estab. Comment: !

AADA:

OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	24-OCT-2000	GMP			EGASM
DO RECOMMENDATION	30-OCT-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
OC RECOMMENDATION	30-OCT-2000		9/23/99	ACCEPTABLE DISTRICT RECOMMENDATION	EGASM
SUBMITTED TO OC	11-JAN-2001				BOALJ
OC RECOMMENDATION	12-JAN-2001			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No:

Responsibilities:

Profile: TCM

Estab. Comment: !  
580) 301-827-4259)

OAI Status: NONE

'S. (on 11-JAN-2001 by J. BOAL (HFD-

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			FERGUSONS
DO RECOMMENDATION	12-JAN-2001			ACCEPTABLE BASED ON FILE REVIEW	MTORRES
OC RECOMMENDATION	12-JAN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment:

DMF No:

Responsibilities:

Profile: CTL

Estab. Comment:

AADA:

OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
OC RECOMMENDATION	23-OCT-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 2650225

ORTHO BIOLOGICS INC  
RD NUMBER 2 KM 46 BO CAMPO ALEGRE  
MANATI, PR 00701

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE STABILITY TESTER  
Profile: CTL OAI Status: NONE  
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
SUBMITTED TO DO	23-OCT-2000	GMP			DAMBROGIOJ
DO RECOMMENDATION	03-NOV-2000			ACCEPTABLE	MTORRES
OC RECOMMENDATION	06-NOV-2000			BASED ON FILE REVIEW ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 2211100

ORTHO PHARMACEUTICAL CORP  
1000 RTE 202  
RARITAN, NJ 08869

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE PACKAGER  
Profile: TCM OAI Status: NONE  
Estab. Comment: RELEASE AND STABILITY TEST OF DRUG SUBSTANCE. PACKAGING OF THE  
BULK DRUG PRODUCT.  
RELEASE AND STABILITY TESTING OF FINISHED DRUG PRODUCT. PACKAGING.  
LABELING. (on 20-OCT-2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
OC RECOMMENDATION	23-OCT-2000			ACCEPTABLE	DAMBROGIOJ
				BASED ON PROFILE	

Establishment: 2242831

ORTHO PHARMACEUTICAL CORP  
NUMBER I CAMPOS DR  
SOMERSET, NJ 08873

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE OTHER TESTER  
INTERMEDIATE STABILITY TESTER  
Profile: CTL OAI Status: NONE  
Estab. Comment: STORAGE AND SAMPLING OF DRUG SUBSTANCES AND EXCIPIENTS. (on 20-  
OCT-2000 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				BOALJ
SUBMITTED TO DO	23-OCT-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	09-NOV-2000	PS			RBROWN4
DO RECOMMENDATION	23-FEB-2001			ACCEPTABLE	NROLI
				BASED ON FILE REVIEW	

THIS SITE SERVES AS ONLY A WAREHOUSE OF RAW MAERIALS AND FINISHED PRODUCT.  
PRODUCT IS TESTED AT ORTHO IN RARITAN CFN # 2211100.

OC RECOMMENDATION 26-FEB-2001

ACCEPTABLE DAMBROGIOJ  
DISTRICT RECOMMENDATION

Establishment: 2650078

ORTHO PHARMACEUTICALS INC  
BO CAMPO ALEGRE  
MANATI, PR 00674

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE STABILITY TESTER

Profile: TCM

OAI Status: NONE

Estab. Comment: MANUFACTURER OF THE OTRHO TRI-CYCLEN 25 TABLETS. (on 20-OCT-2000  
by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-OCT-2000				DAMBROGIOJ
SUBMITTED TO DO	23-OCT-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	03-NOV-2000			ACCEPTABLE	MTORRES
OC RECOMMENDATION	06-NOV-2000			BASED ON FILE REVIEW ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment:

DMF No:

AADA:

Responsibilities:

Profile: CTL

OAI Status: NONE

Estab. Comment: JAN-2001 by J. BOAL (HFD-580) 301-827-4259 . (on 12-

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-2001				BOALJ
SUBMITTED TO DO	12-JAN-2001	GMP			FERGUSONS
DO RECOMMENDATION	01-FEB-2001			ACCEPTABLE	MFADDEN

OC RECOMMENDATION 02-FEB-2001

ACCEPTABLE FERGUSONS  
DISTRICT RECOMMENDATION

Establishment:

DMF No:

AADA:

Responsibilities:

14-JUN-2001

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Page 6 of 6

Profile: CTL OAI Status: NONE  
Estab. Comment: 580) 301-827-4259 (on 12-JAN-2001 by J. BOAL (HFD-

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JAN-2001				BOALJ
OC RECOMMENDATION	12-JAN-2001			ACCEPTABLE BASED ON PROFILE	FERGUSONS

APPEARS THIS WAY  
ON ORIGINAL

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-241**DATE REVIEWED:** April 13, 2001**CHEMISTRY REVIEW #:** 1**REVIEWER:** Jila H. Boal

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
ORIGINAL	August 25, 2000	August 29, 2000	September 1, 2000
Amendment	November 8, 2000	November 9, 2000	
Amendment	January 22, 2001	January 23, 2001	
Amendment	March 27, 2001	March 28, 2001	
Amendment	April 5, 2001	April 6, 2001	
Amendment	May 11, 2001	May 14, 2001	

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME**Proprietary:

ORTHO TRI-CYCLEN®Lo

Nonproprietary/Established/USAN:

Norgestimate / Ethinyl estradiol

Code Name/#:

None

Chem.Type/Ther.Class:

3S

**PHARMACOL. CATEGORY/INDICATION:**

Prevention of pregnancy in women who elect to use oral contraceptive as a method of contraception

**DOSAGE FORM:**

Tablet

**STRENGTHS:**

180 µg norgestimate / 25 µg ethinyl estradiol  
215 µg norgestimate / 25 µg ethinyl estradiol  
250 µg norgestimate / 25 µg ethinyl estradiol

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:** Rx  OTC**SPECIAL PRODUCTS** Yes  No

( If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

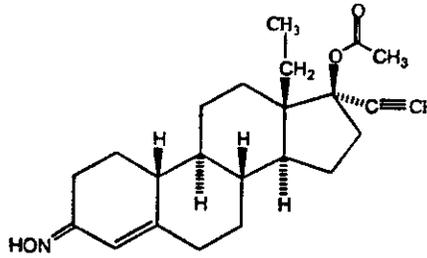
Norgestimate

a. 18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 $\alpha$ )- (+)-b. (+)-13-Ethyl-17-hydroxy-18, 19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime acetate (ester)Molecular Formula: C<sub>23</sub>H<sub>31</sub>NO<sub>3</sub>

Molecular weight —

CAS Registry Number: 35189-28-7

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Ethinyl Estradiol:

a. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-

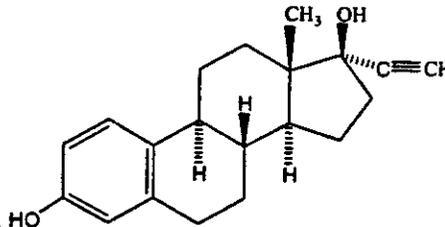
b. 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular Formula:  $C_{20}H_{24}O_2$

Molecular weight: \_\_\_\_\_

CAS Registry Number: 57-63-6

APPEARS THIS WAY  
ON ORIGINAL



**SUPPORTING DOCUMENTS:**

DMF Type/Number	Subject	Holder	Status	Review Date / Reviewed by	Letter Date
			Active	N/A	N/A
			Active	N/A	N/A
			Adequate	October 18, 1999/ Dr. A. Alhakim,	N/A
			Adequate	May 23, 2001/ Dr. Jila H. Boal	NA
			Adequate	July 17, 2000/ Dr. David T. Lin	N/A
			Adequate	September 14, 1999/ Dr. Jila H. Boal	N/A
			Adequate	September 27, 2000/ Dr. Richard T. Lostritto (DMF Stricke Force)	N/A
			Adequate	March 28, 2001/	N/A

			Dr. Jila H. Boal	
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**RELATED DOCUMENTS (if applicable):**

NDA # 19-653, ORTHO-CYCLEN®  
 NDA # 19-697, ORTHO TRI-CYCLEN®  
 NDA # 21-040, ORTHO-PREFEST™

**CONSULTS:**

- 1. Microbiology:** Not applicable. This product is solid oral dosage form.
- 2. EER:** Was sent on October 2000 for facilities involved and an overall "acceptable" rating was recommended on April 12, 2001.
- 3. Trademark:** At first, sponsor proposed the trademark \_\_\_\_\_ for this product. Later prior to submission of the NDA, RWJPRI determined that the trademark \_\_\_\_\_ would be more appropriate, therefore on April 10, 2000 sponsor submitted the proposed name \_\_\_\_\_ to OPDRA. \_\_\_\_\_ was not accepted by OPDRA.

The OPDRA's conclusion is conveyed to the sponsor through an information request letter dated January 24, 2001. Later, the new name ORTHO TRI-CYCLEN® Lo was proposed. OPDRA objected to this name and recommended the trademark of: \_\_\_\_\_. Amendment of March 27, 2001 is request for reconsideration and acceptance of the trademark ORTHO TRI-CYCLEN® Lo. DRUDP reviewed the amendment of March 27<sup>th</sup>, and finds the proposed trademark ORTHO TRI-CYCLEN Lo to be acceptable.

**REMARKS/COMMENTS:**

The active compounds in this tri-phasic regimen of oral contraceptive drug product tablets are norgestimate \_\_\_\_\_ and ethinyl estradiol, USP (\_\_\_\_\_.). These same drug substances (\_\_\_\_\_) are used in the approved marketed products ORTHO-CYCLEN® (NDA 19-653) and ORTHO TRI-CYCLEN® (NDA 19-697). Norgestimate \_\_\_\_\_ is also used in the approved marketed product ORTHO-PREFEST™ (NDA 21-040).

The drug product will be packaged for commercial sale in blister ring with foil over wrap. After opening the foil wrap the user will place the blister ring in a DIALPAK® Tablet Dispenser for use. Each blister ring contains white NGM (180 µg) / EE (25 µg) tablets (Days 1 to 7), light blue NGM (215 µg) / EE (25 µg) tablets (Days 8 to 14), dark blue NGM (250 µg) / EE (25 µg) tablets (Days 15 to 21), and green placebo tablets (Days 22 to 28). The tablets are debossed, round, and coated convex tablets.

The applicant is proposing this new estrogen/progesterone combination tablet to be a lower dose estrogen method of oral contraception as compared to ORTHO TRI-CYCLEN.

Amendment dated November 8, 2000 contains additional 3 months stability data for drug product. This extends the results of primary stability batches to 12 months.

The amendment also includes correction to the contract testing laboratories as follow:

Amendment of January 22, 2001 is response to the Division's January 12, 2001 letter, requesting to clarify the responsibilities / addresses of the facilities involved in the drug product manufacture.

Amendment of March 1, 2001 is a revision to the amendment of January 22, 2001 to remove the site, Ortho-McNeil Pharmaceutical, Inc. at Spring House, Pennsylvania; and to assign the responsibilities of this facility to Ortho-McNeil Pharmaceutical, Inc. in Raritan New Jersey. Applicant has submitted revised tables with the relevant information. The final revised information is reported to the EER (see EER Report in Appendix A).

Amendment of March 27, 2001 is request for reconsideration and acceptance of the trademark ORTHO TRI-CYCLEN<sup>®</sup> Lo. Final decision from DRUDP on trademark is ORTHO TRI-CYCLEN<sup>®</sup> Lo.

Amendment of April 5, 2001 is submission of 18-month drug product stability data at 25°C/60% RH and additional data at the condition of 30°C/60% RH for up to 18-month to conform to ICH.

Amendment of May 11, 2001 is revision of the packaging components to reflect the newly accepted trademark ORTHO TRI-CYCLEN<sup>®</sup> Lo and submission of the color copies of the proposed blister ring, foil over wrap and packer (front and back) for the finished drug product.

Sponsor proposes \_\_\_\_\_ when drug product is labeled "\_\_\_\_\_  
excursions permitted to \_\_\_\_\_

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

\_\_\_\_\_  
Jila H. Boal, Ph.D., Review Chemist

cc:  
Org. NDA 21-241  
HFD-580/Division File  
HFD-580/BoalJ  
HFD-580/MercierJ  
HFD-580/RheeM  
R/D Init by:  
filename: NDA 21-241 Review # 1

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HFD-580-RheeM/BoalJ  
HFD-580-MercierJ  
HFD-580-AllenS

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NDA 21-241

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

Jonson & Johnson Pharmaceutical Research Institute  
3S

PM: Jennifer Mercier  
HFD-580  
7-4260

U  
ISI  
8/22/02

DMF Review

N/A

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