CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020681

Trade Name : ORTHO TRI-CYCLEN TABLETS

Generic Name: Norgestimate and Ethinyl Estradiol

Sponsor : R. W. Johnson Pharmaceutical Research Institute

Approval Date: December 31, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-681

DEC 31 1996

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

Dear Ms. Jordan:

Please refer to your December 26, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ortho Tri-Cyclen (norgestimate/ethinyl estradiol) Tablets.

Please refer to your approvable letter dated December 6, 1996.

We acknowledge receipt of your amendments dated December 5 and 10, 1996.

This new drug application provides 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.

We have completed the review of this application, as amended, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed final version of the labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revision of the labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-681. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or

mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA. To comply with these regulations, all 3-day and 15-day alert reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 19-697 for this drug product, not to this NDA. This includes the quarterly periodic adverse drug experience reports required by this new NDA. In the future, no submissions should be made to this NDA except for the 16 copies of the final printed labeling, as requested above.

If you have any questions, please contact:

Kevin Darryl White, M.B.A.
Project Manager
(301) 827-2023

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-681 Supplement # ____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF D- 540 Trade (generic) name/dosage form: ORTHO TRI_CYCLEN (norgestimate/ethinyl estradiol) Action: (AP) AE NA 12/21/96

Applicant R.W. Johnson PRI Therapeutic Class Hormonal Agent

Indication(s) previously approved Prevention of pregnany in women who elect to use oral contraceptives as a method of contraception

Pediatric labeling of approved indication(s) is adequate (X) inadequate ____

Indication in this application Treatment of moderate acne vulgaris in females, ≥ 15YOA, who have no contraindications to oral contraceptive therapy, have achieved menarche, (on back)

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

(X) 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM

[signature] 12/20/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

[signature] 12/31/96

cc: Orig NDA/PLA # 20-681
HF D-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Indication in this application (con't):
unresponsive to topical anti-acne medications and desire contraception.

EXPLAIN:

The pivotal studies included pediatric patients at 15 YOA and above. Pediatric patients younger than 15 YOA would have less potential use of this drug product.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-681 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: ORTHO TRI-CYCLEN 1 MG NORGESTIMATE/ETHINYL ESTRADIOL Action: (AP) AE ~~AA~~

Applicant R.W. JOHNSON PRI Therapeutic Class HORMONAL AGENT

Indication(s) previously approved PREVENTION OF PREGNANCY IN WOMEN WHO ELECT TO USE ORAL CONTRACEPTIVES AS A METHOD OF CONTRACEPTION

Pediatric labeling of approved indication(s) is adequate X inadequate ___

Indication in this application TREATMENT OF MODERATE ACNE VULGARIS IN FEMALES, ≥15 YOA, WHO HAVE NO CONTRAINDICATIONS TO ORAL CONTRACEPTIVE THERAPY HAVE ACHIEVED MENARCHE AND ARE UNRESPONSIVE TO TOPICAL ANTI-ACNE MEDICATIONS AND DESIRE CONTRACEPTION

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

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- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

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___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

✓ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] 12/6/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig (NDA)/PLA # 20-681
HFD-540/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Pivotal

The pivotal studies included pediatric patients at 15 YOA and above. Pediatric patients younger than 15 YOA would have less potential use of this drug product.

12/6/96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-681

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

DEC 6 1996

Dear Ms. Jordan:

Please refer to your December 26, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ortho Tri-Cyclen (norgestimate/ethinyl estradiol) Tablets.

We acknowledge receipt of your amendments dated January 17 and 24, March 15, April 12 and 26, October 7, 23, 29 and 31, and November 11 and 19, 1996.

We have completed the review of this application, as amended, including the submitted draft labeling, and it is approvable. Before the application may be approved, it will be necessary for you to submit draft labeling for the drug product as recommended in the enclosed, revised, draft labeling.

Should additional information relating to the safety and effectiveness of the drug become available, further revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

This drug may not be legally marketed (for the treatment of acne vulgaris) until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Kevin Darryl White, M.B.A.
Project Manager
(301) 827-2023

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

CERTIFICATION REQUIREMENT FOR APPROVAL OF A DRUG PRODUCT

The R.W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or 306 (b) of the Federal Food Drug and Cosmetic Act, in connection with this NDA.

XIII. PATENT INFORMATION

NDA 20-681

ORTHO TRI-CYCLEN TABLETS
(norgestimate/ethinyl estradiol)

The patent status of ORTHO TRI-CYCLEN Tablets is as follows:

ORTHO TRI-CYCLEN is protected by:

U.S. Patent No.:	4,027,019
Expiration Date:	July 24, 1997*
U.S. Patent No.:	4,530,839
Expiration Date:	September 26, 2003**
U.S. Patent No.:	4,544,554
Expiration Date:	September 26, 2003**
U.S. Patent No.:	4,616,006
Expiration Date:	July 23, 2002
U.S. Patent No.:	4,628,051
Expiration Date:	September 26, 2003**

U.S. Patent No. 4,027,019 claims the D-isomer of norgestimate, U.S. Patent Nos. 4,530,839 and 4,544,554 claim a triphasic regime in which the progestin is norgestimate and U.S. patent No. 4,616,006 claims a composition for use in a triphasic regime in which norgestimate is the progestin. U.S. Patent No. 4,628,051 claims a triphasic regime in which the progestin in norgestimate and a composition for use in a triphasic regime in which norgestimate is the progestin.

* By action of the Uruguay Round Agreements Act, Public Law 103-465, which was signed by the President of the United States on December 8, 1994, the original expiration date of the above patent was changed to July 24, 1995; to this date is added a 730 day extension under the Hatch-Waxman Amendments, 35 USC 156, which brings the expiration date to July 24, 1997.

** By action of the Uruguay Round Agreements Act, Public Law 103-465, which was signed by the President of the United States on December 8, 1994, the original expiration date of the above patent was changed to September 26, 2003.

Medical Officer's Review of NDA 20-681

Submission Date:	December 26, 1995	NOV 19 1996
Receipt Date:	January 4, 1996	
First Draft:	October 11, 1996	
Ninth Draft:	November 19, 1996	
Sponsor:	R. W. Johnson Route 202, Box 300 Raritan, New Jersey 08869	
Trade Name:	ORTHO TRI-CYCLEN	
Generic Name:	Norgestimate and ethinyl estradiol	
Pharmacologic Category:	Oral Contraceptive	
Dosage Form:	Oral	
Proposed Indication:	Acne Vulgaris in Females	
Proposed Dosage:	Once daily	
Related NDA's:	19-697 Related IND's: 19-653	

Marketing History: ORTHO TRI-CYCLEN is marketed as an oral contraceptive in the United States and nine foreign countries (Austria, Brazil, Canada, Colombia; Germany, Italy, Portugal, Slovenia and South Africa).

Rationale: Research has suggested a possible link between androgens and the development of acne; it is well known that androgens stimulate the sebaceous glands. It is felt that estrogens may exert an anti-acne effect by 1) suppressing the secretion of pituitary gonadotrophin thereby inhibiting the production of androgens or by 2) enhancing the binding of testosterone to sex hormone binding globulin and rendering the bound testosterone inactive.

The sponsor proposes that norgestimate which has a low concentration of progestins (.250mg) in combination with ethinyl estradiol, would be a safe and effective anti-acne medication.

Pharmacology: No new pharmacologic data was submitted.
See review by Amy Norstrandt

Chemistry: No new manufacturing data was submitted.
See review by Ernie Pappas

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Human Efficacy and Safety Studies

Two identically designed United States multicenter studies (N93-034 and N93-035) were submitted in support of this NDA.

Methods: Adult female patients who met the study entry criteria were randomly enrolled into a 6 month double-blind trial. Evaluations for the primary and secondary efficacy parameters, as well as safety, consisted of 9 clinic visits that were completed according to the following schedule:

Visit 1 - prestudy-admission
Visit 2 - 6 (days 17 to 24 of the patients menstrual cycle
Visit 7 - 9 (cycle days 1 to 8, 8 to 14 and 17 to 24)

Patients enrolled in the active arm of the trial were given a Dialpak containing a 28-day cycle of treatment (21 days of ORTHO TRI-CYCLEN and 7 days of inactive drug). The placebo group received an identical appearing Dialpak, containing 28 days of a color matched placebo.

Safety monitoring consisted of grading the impact of the occurrence of adverse events:

Mild	-	Minimal impact
Moderate	-	Noticeable impact
Marked	-	Substantial impact

Primary efficacy parameters consisted of the:

1) change in inflammatory lesion count from baseline to the last available evaluation;

2) change in total lesion count from baseline to the last available evaluation;

3) percentage of subjects showing improvement (fair, good or excellent progress versus no change or worse) on the investigator's global assessment.

Secondary efficacy parameters consisted of the:

1) subject's self-assessment
   a) subject's end of therapy assessment of acne improvement,
   b) subject's comparison to prior acne treatment at end of therapy,
   c) subject's desire to continue study treatment at study termination;

2) within cycle analysis of inflammatory and total lesions;

3) individual lesion counts: comedones (open and closed), papules, pustules, nodules; and

4) change in hormone levels from baseline. (Study N93-034 only)

Inclusion Criteria:

Moderate facial acne with 6-100 comedones and 10-50 papules or pustules (the total number of nodules could not exceed 5).

Gynecologic examination with the preceding 6 months showing a normal PAP smear.

Negative urine pregnancy test at enrollment.

Patients between 35 and 49 years were required to be non-smokers.

Discontinuation prior to enrollment: oral contraceptives and Norplant - 3 months, Depo-Provera and systemic retinoids - 6 months, systemic antimicrobials - 1 month and topical acne preparations - 2 weeks.

Patients of child bearing potential using bearier/non-hormonal contraceptive .

Avoidance of comedogenic make-up, sunscreens and anti-acne therapy.

Exclusion Criteria:

Pregnancy, lactation.

Significant renal, hepatic, cardiovascular, hematologic, neurologic, malignant, psychiatric, respiratory, metabolic or hypertensive disease or other medical condition/therapy which may be exacerbated by the treatment or interfere with interpretation of study results.

Known sensitivities to any of the study materials.

Receipt of an experimental drug within 30 days of study entry.

Contraindications to oral contraceptives.

Study N93-034: A Double-Blind, Multicenter, Placebo Controlled Study Evaluating the Efficacy of ORTHO TRI-CYCLEN in the Treatment of Moderate Acne Vulgaris.

Two-hundred fifty female patients aged 15 to 49 years were randomized into the study. Demographics are provided on the evaluable population (Tables 1 and 2).

Table 1. Demographics - Age and Ethnic Group

Demographic Characteristics			Treatment		
			ORTHO TRI-CYCLEN	Placebo	TOTAL
Age at Enrollment (years)		N	118	113	231
		Mean	28.36	28.42	28.39
		SD	8.04	7.40	7.72
		Minimum	15	15	15
		Median	26.36	28.27	27.23
		Maximum	49	47	49
Ethnic Origin	Caucasian	N	99	89	188
		%	83.9	78.8	81.4
	Black	N	13	16	29
		%	11.0	14.2	12.6
	Oriental	N	2	3	5
		%	1.7	2.7	2.2
	Hispanic	N	4	5	9
		%	3.4	4.4	3.9
	Other	N	0	0	0
		%	0	0	0

Table 2. Demographics - Age Onset of Acne and Weight in Pounds

Demographic Characteristics		Treatment		
		ORTHO TRI-CYCLEN	Placebo	TOTAL
Age at Onset of Acne (years)	N	118	113	231
	Mean	14.36	15.71	15.02
	SD	4.34	6.49	5.53
	Minimum	8	10	8
	Median	13.00	13.00	13.00
	Maximum	37	46	46
Weight (lbs)	N	117	111	228
	Mean	146.36	140.99	143.75
	SD	35.02	29.21	32.36
	Minimum	96	96	96
	Median	140.00	133.00	135.00
	Maximum	283	240	283

Reviewer's Comments: The patients were demographically balanced between the two treatment groups relative to age, race and duration of disease.

Study N93-034 Cont'd
Baseline and end of therapy hormonal parameters (total testosterone, free testosterone, sex hormone binding globulin [SHBG] and dehydroepiandosterone sulfate [DHEAS]) were measured at 6 selected centers in order to assess a correlation or alteration with treatment and response. (This assessment was only undertaken in Study N93-034)

Two-hundred thirty-one subjects were evaluable for safety; 118 of whom were randomized to the ORTHO TRI-CYCLEN group, 113 were randomized to the placebo group.

One-hundred seventy-nine patients completed the study: 92 in the ORTHO TRI-CYCLEN group and 87 in the placebo group. Fifty-two patients discontinued: 26 (22%) of whom were in the ORTHO TRI-CYCLEN group and 26 (23%) of whom were in the placebo group.

Eighteen of the premature discontinuations were for an adverse event: 13 or(11%) of the ORTHO TRI-CYCLEN group and 5 (4.4%) of the placebo group. The adverse events were not serious and included (ORTHO TRI-CYCLEN - nausea, headache, breast tenderness, hot flashes, weight gain; placebo - headache, weight gain, nausea, depression). Four subjects in the ORTHO TRI-CYCLEN group and 0 subjects in the placebo group terminated because of an exacerbation of acne (Table 3).

Table 3. Disposition of Subjects

		Treatment				Total	
		ORTHO TRI-CYCLEN		Placebo			
		N	%	N	%	N	%
Number of Subjects Exposed		118	100.0	113	100.0	231	100.0
Total Completed		92	78.0	87	77.0	179	77.5
Total Discontinued		26	22.0	26	23.0	52	22.5
Reason for Early Termination	Adverse Event	13	11.0	5	4.4	18	7.8
	Significant Exacerbation of Acne	4	3.4	0	0	4	1.7
	Significant Protocol Violation	2	1.7	7	6.2	9	3.9
	Subject's Request	1	0.8	6	5.3	7	3.0
	Intercurrent Illness	0	0	0	0	0	0
	Lost to Follow-up	5	4.2	5	4.4	10	4.3
	Other	1	0.8	3	2.7	4	1.7

Reviewer's Comments: Although the total number of patients discontinued were equal between the two groups, the number of adverse events in the ORTHO TRI-CYCLEN group (13/11%) was greater than placebo (5/4.4%). The majority of these events involved the reproductive system and consisted of breast tenderness or enlargement and intermenstrual bleeding. Protocol violations included the use of non-study anti-acne drugs, which occurred to a greater extent in the placebo treated patients. Discontinuances due to exacerbation of acne were greater in the ORTHO TRI-CYCLEN treated group (4 versus 0), the p value of which was 0.038 .

Study N93-034 Cont'd

Efficacy analyses were performed on 1) the "intent-to-treat" population (227 patients who took the study medication and had at least one on therapy efficacy assessment) and 2) the "evaluable" population (164 patients who completed the study and did not have major protocol variations) (Table 4). Data sets for both populations are contained in this review.

Table 4. Intent-to-Treat and Evaluable Patients for Efficacy

Subject Evaluability		Treatment				Total	
		ORTHO TRI-CYCLEN		Placebo			
		N	%	N	%	N	%
Evaluable		84	73.7	80	70.8	164	72.2
Non-Evaluable		30	26.3	33	29.2	63	27.8
Reason Non-Evaluable	Did Not Complete Study	22	19.3	26	23.0	48	21.1
	Non-Allowed Concurrent Medication During Study	6	5.3	4	3.5	10	4.4
	Inadequate Lesion Count at Enrollment	2	1.8	2	1.8	4	1.8
	Non-Allowed Concurrent Medication Use During Study; Inadequate Washout of Pre-Study Medications	0	0.0	1	0.9	1	0.4
Total		114	100.0	113	100.0	227	100.0

Reviewer's Comments: The numbers and percentages of patients who were evaluable-for-efficacy and who constituted the intent-to-treat populations were equal between the two groups.

Study N93-034 Cont'd

Investigators:

Brenda Berberian, MD
Georgetown University Hospital
3900 Reservoir Road
Washington, DC 20007

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Geoffrey Redmond, MD
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23200 Chagrin Boulevard
Beachwood, Ohio 44122

Results - Primary Efficacy Variables Study N93-034

Table 5. Change in Inflammatory Lesion Count from Baseline

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	18.99	9.65	9.34	10.97	-17.00	9.00	69.00	114	45.43	44.02	-121.43	58.58	100.00
	Placebo	113	18.92	12.25	6.67	11.17	-40.00	6.00	71.00	113	31.48	45.99	-200.00	40.00	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	18.65	8.74	9.92	9.26	-17.00	10.00	44.00	84	51.41	42.13	-121.43	61.72	100.00
	Placebo	80	18.99	12.06	6.93	9.85	-40.00	7.00	41.00	80	34.55	44.29	-200.00	41.06	100.00

Reviewer's Comments: The baseline mean counts of inflammatory lesions (papules, pustules and nodules) were equal in placebo and ORTHO TRI-CYCLEN treated groups. In the intent-to-treat population the mean change from baseline for the ORTHO TRI-CYCLEN treated groups was 9.34, resulting in a p-value of 0.0203 when compared to the mean change in the placebo group of 6.67. Similarly, review of the data submitted for the evaluable-for-efficacy group revealed an advantage (p-value 0.0096) of ORTHO TRI-CYCLEN (mean change 9.92) versus placebo (6.93).

Table 6. Change in Total Lesion Count from Baseline

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	55.88	32.04	23.83	26.45	-58.00	21.00	128.00	114	39.54	34.70	-85.29	46.66	95.12
	Placebo	113	56.53	37.21	19.32	24.43	-45.00	17.00	119.00	113	31.93	33.55	-86.54	38.10	86.23
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	53.86	26.11	27.75	24.23	-29.00	25.50	106.00	84	46.44	31.38	-85.29	52.98	95.12
	Placebo	80	54.49	35.36	19.13	21.08	-45.00	18.00	105.00	80	33.93	33.00	-86.54	38.68	83.56

Reviewer's Comments: The change in total lesion count (inflammatory lesions plus comedones) approached but did achieve statistical significance in the ORTHO TRI-CYCLEN group when compared to the placebo treated group (p=0.076); the mean changes respectively were 23.8 and 19.8. More apparent differences (p = 0.0007) occurred in the evaluable-for-efficacy comparisons, where the mean change in the ORTHO TRI-CYCLEN group was 27.6 (a decrease of approximating 50% from baseline) versus a mean change of 19.3 in the placebo group.

Results Primary Efficacy Variables Study N93-034 Cont'd

Table 7. Investigator's Global Assessment (Intent-to-Treat)

Global Progress of Treatment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Excellent	26	22.8	8	7.1
	Good	38	33.3	34	30.1
	Fair	25	21.9	27	23.9
	Subtotal	89	78.1	69	61.1
Not Improved	No Change	13	11.4	36	31.9
	Worse	12	10.5	8	7.1
	Subtotal	25	21.9	44	38.9
Total		114	100.0	113	100.0

Reviewer's Comments: The investigator's assessment of improved versus not improved between the two groups was significantly ($p=0.004$) in favor of the ORTHO TRI-CYCLEN treated patients with 89 (78%) showing improvement compared to 69 (61%) of the placebo group. An excellent grade was received by 26 (23%) of the ORTHO TRI-CYCLEN patients versus 8 (7%) of the placebo group (p-value = 0.01). Similarly, 39% of the placebo patients were graded as not improved versus 22% of the ORTHO TRI-CYCLEN patients, resulting in a p-value of <0.001 for all five scales.

Table 8. Investigator's Global Assessment (Evaluable-for-Efficacy)

Global Progress of Treatment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Excellent	22	26.2	6	7.5
	Good	32	38.1	25	31.3
	Fair	16	19.0	19	23.8
	Subtotal	70	83.3	50	62.5
Not Improved	No Change	9	10.7	25	31.3
	Worse	5	6.0	5	6.3
	Subtotal	14	16.7	30	37.5
Total		84	100.0	80	100.0

Reviewer's Comments: The results obtained in the evaluable-for-efficacy population were not dissimilar from those obtained in the intent-to-treat group; 83% of the ORTHO TRI-CYCLEN patients were graded as improved compared to 63% of the placebo patients (p-value <0.001). The difference between groups for improved versus not improved significantly favored ORTHO TRI-CYCLEN ($p=0.001$).

Results Secondary Efficacy Variables N93-034 Cont'd

Subject's End of Therapy Self-Assessment of Acne Improvement

Table 9a) Intent-to-Treat

Subject Self-Assessment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Much Improved	33	31.1	13	12.5
	Somewhat Improved	45	42.5	35	33.7
	Subtotal	78	73.6	48	46.2
Not Improved	Not Improved	17	16.0	48	46.2
	Worse	8	7.5	8	7.7
	Much Worse	3	2.8	0	0
	Subtotal	28	26.4	56	53.8
Total		106	100.0	104	100.0

Table 9b) Evaluable-for-Efficacy

Subject Self-Assessment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Much Improved	30	36.1	10	12.5
	Somewhat Improved	38	45.8	28	35.0
	Subtotal	68	81.9	38	47.5
Not Improved	Not Improved	10	12.0	37	46.3
	Worse	5	6.0	5	6.3
	Much Worse	0	0	0	0
	Subtotal	15	18.1	42	52.5
Total		83	100.0	80	100.0

Reviewer's Comments: A statistically significant difference ($p < 0.001$) was demonstrated in both the intent-to-treat and evaluable-for-efficacy results favoring ORTHO TRI-CYCLEN over placebo in the patient's assessment of the degree of improvement in acne.

Subject's Comparison to Prior Acne Treatment at Study Termination

Table 10a) Intent-to-Treat

Comparison to Prior Acne Treatment	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
Better	44	41.5	26	25.0
The Same	25	23.6	28	26.9
Worse	22	20.8	34	32.7
Not Applicable	15	14.2	16	15.4
TOTAL	106	100.0	104	100.0

Table 10b) Evaluable-for-Efficacy

Comparison to Prior Acne Treatment	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
Better	40	48.2	22	27.5
The Same	23	27.7	20	25.0
Worse	12	14.5	26	32.5
Not Applicable	8	9.6	12	15.0
TOTAL	83	100.0	80	100.0

Reviewer's Comments: When asked to compare the study treatment with previous acne therapy, 65% of the intent-to-treat and 75% of the evaluable-for-efficacy patients treated with ORTHO TRI-CYCLEN stated that ORTHO TRI-CYCLEN was better or the same as opposed to 51% and 53% of the placebo group, respectively. Statistical analysis demonstrated a significant difference (p-value = 0.005) favoring ORTHO TRI-CYCLEN.

Results Secondary Variables Study P93-034 Cont'd

Subject's Desire to Continue Study Treatment at Study Termination

Table 11a) Intent-to-Treat

Would Subject Continue ORTHO TRI-CYCLEN	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
No	38	35.8	62	59.6
Yes	68	64.2	42	40.4
TOTAL	106	100.0	104	100.0

Table 11b) Evaluable-for-Efficacy

Would Subject Continue ORTHO TRI-CYCLEN?	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
No	25	30.1	47	58.8
Yes	58	69.9	33	41.3
TOTAL	83	100.0	80	100.0

Reviewer's Comments: Similar to the previous patient subjective responses; greater percentages and numbers of ORTHO TRI-CYCLEN treated patients (67.5%) stated that they would continue ORTHO TRI-CYCLEN therapy. Forty percent of placebo treated patients would continue, the statistical significance of which resulted in a p-value of <0.0001.

Results Secondary Efficacy Variables P93-034 Cont'd

Table 12. Within Cycle Analysis of Inflammatory and Total Lesions
Intent-to-Treat

Lesion Count	Treatment	N	Baseline Mean	Mean (Cycle 6, Week 1)	Mean (Cycle 6, Week 2)	Mean (Cycle 6, Week 3)	P-value for Hotelling's T^2 Test
Inflammatory Lesions	ORTHO TRI-CYCLEN	73	19.79	8.82	8.86	8.52	0.8095
	Placebo	74	19.69	12.62	12.15	11.55	0.3433
Total Lesions	ORTHO TRI-CYCLEN	73	57.08	27.15	26.56	26.53	0.8393
	Placebo	74	57.35	39.84	38.58	35.36	0.1031
Total Comedones	ORTHO TRI-CYCLEN	73	37.29	18.33	17.70	18.01	0.7619
	Placebo	74	37.66	27.22	26.43	23.81	0.1489

Table 13. Within Cycle Analysis of Inflammatory and Total Lesions
Evaluable-for-Efficacy

Lesion Count	Treatment	N	Baseline Mean	Mean (Cycle 6, Week 1)	Mean (Cycle 6, Week 2)	Mean (Cycle 6, Week 3)	P-value for Hotelling's T^2 Test
Inflammatory Lesions	ORTHO TRI-CYCLEN	67	19.13	8.76	9.06	8.75	0.8559
	Placebo	68	19.26	12.87	12.24	11.74	0.3695
Total Lesions	ORTHO TRI-CYCLEN	67	55.93	26.49	26.03	26.27	0.9343
	Placebo	68	55.43	40.54	38.51	35.85	0.1155
Total Comedones	ORTHO TRI-CYCLEN	67	36.79	17.73	16.97	17.52	0.6764
	Placebo	68	36.16	27.68	26.28	24.12	0.1576

Reviewer's Comments: There were no statistically significant within cycle differences demonstrated in the intent-to-treat or evaluable-for-efficacy groups for either therapy.

Results Secondary Efficacy Parameters N93-034 Cont'd

Table 15. Mean Change Open Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	16.25	8.12	8.12	16.40	-23.00	3.00	89.00	96	39.41	69.45	-383.33	56.92	100.00
	Placebo	113	13.81	7.55	6.27	14.58	-22.00	3.00	93.00	102	20.02	102.66	-600.00	41.15	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	14.33	6.80	7.54	17.24	-23.00	2.50	89.00	70	37.39	75.02	-383.33	60.00	100.00
	Placebo	80	12.86	7.08	5.79	15.06	-22.00	2.50	93.00	71	16.72	116.76	-600.00	48.72	100.00

Table 16. Mean Change Closed Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	20.64	14.27	6.37	15.49	-64.00	5.00	46.00	112	19.03	72.75	-283.33	41.29	100.00
	Placebo	113	23.80	17.42	6.38	14.34	-36.00	5.00	49.00	109	15.58	76.05	-433.33	38.00	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	20.87	10.57	10.30	13.35	-20.00	7.00	46.00	82	31.91	67.20	-283.33	50.00	100.00
	Placebo	80	22.64	16.23	6.41	13.72	-36.00	6.00	49.00	76	19.48	79.30	-433.33	41.42	100.00

Table 17. Mean Change Total Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	36.89	22.39	14.49	20.43	-41.00	11.00	75.00	114	32.55	54.39	-271.43	43.05	96.55
	Placebo	113	37.61	24.96	12.65	20.62	-58.00	10.00	110.00	113	31.36	45.35	-207.14	38.36	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	35.20	17.37	17.83	20.17	-38.00	14.00	75.00	84	39.43	57.09	-271.43	50.00	96.55
	Placebo	80	35.50	23.30	12.20	19.47	-58.00	10.50	96.00	80	33.78	48.14	-207.14	41.21	100.00

Reviewer's Comments: In the intent-to-treat populations there was a decrease in the mean number of open and closed comedones in both treatment groups favoring ORTHO TRI-CYCLEN. The decrease was not statistically significant (p-values of 0.936 and 0.034, respectively). Similar results were obtained in the evaluable-for-efficacy analysis; except there was a significant advantage ($p = 0.0056$) in the ORTHO TRI-CYCLEN group resulting from the greater decrease in the mean number of closed comedones. The p-values for open comedones and total comedones were 0.720 and 0.0184, respectively.

Results Secondary Efficacy Parameters N93-034 Cont'd

Table 18. Mean Change for Papules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	15.43	8.01	7.42	9.79	-17.00	8.00	63.00	114	36.63	64.12	-300.00	54.20	100.00
	Placebo	113	15.48	10.14	5.34	8.72	-40.00	6.00	36.00	113	28.83	58.34	-350.00	41.38	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	14.87	7.50	7.37	8.18	-17.00	8.50	31.00	84	39.33	69.16	-300.00	60.36	100.00
	Placebo	80	15.74	9.76	5.98	8.28	-40.00	6.00	36.00	80	36.45	41.66	-200.00	46.06	100.00

Table 19. Mean Change for Pustules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	3.30	1.51	1.79	4.16	-13.00	1.00	16.00	79	52.28	83.03	-433.33	90.00	100.00
	Placebo	113	3.07	1.78	1.29	5.12	-21.00	0.00	35.00	65	31.74	102.27	-600.00	63.64	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	3.52	1.14	2.38	4.24	-5.00	1.00	16.00	57	65.25	63.03	-150.00	100.00	100.00
	Placebo	80	2.90	1.91	0.99	4.49	-21.00	0.00	16.00	44	26.60	117.56	-600.00	61.82	100.00

Table 20. Mean Change for Nodules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	114	0.26	0.13	0.13	0.81	-3.00	0.00	4.00	17	97.35	7.52	75.00	100.00	100.00
	Placebo	113	0.37	0.33	0.04	0.84	-4.00	0.00	3.00	24	58.33	60.79	-100.00	100.00	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	84	0.26	0.10	0.17	0.80	-3.00	0.00	4.00	13	98.46	5.55	80.00	100.00	100.00
	Placebo	80	0.35	0.39	-0.04	0.95	-4.00	0.00	3.00	14	42.86	68.47	-100.00	83.33	100.00

Reviewer's Comments: In both the intent-to-treat and evaluable-for-efficacy populations the mean decrease in papules was statistically greater in the ORTHO TRI-CYCLEN group than in the placebo group (p-values = 0.0218 and 0.0457, respectively). There was no significant advantage demonstrated in the mean change for pustules (p = 0.467) or nodules (p = 0.095) in the intent-to-treat or evaluable-for-efficacy patients (p = 0.0693 [pustules] and p = 0.120 [nodules]) favoring ORTHO-TRI-CYCLEN.

Results Secondary Efficacy Parameters Study N93-034 Cont'd

Table 21. Change in Androgen and SHBG from Baseline to Last Available Evaluation

Androgens and SHBG	Treatment															
	ORTHO TRI-CYCLEN								Placebo							
	N	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change
Total Testosterone (ng/dl)	73	32.45	32.34	-0.11	14.08	-26.00	-2.00	43.00	69	32.09	36.25	4.16	19.75	-44.00	2.00	98.00
Free Testosterone (pg/ml)	73	4.30	2.24	-2.05	3.54	-15.20	-1.30	8.00	69	3.71	4.15	0.44	2.79	-10.10	0.10	9.50
% Free Testosterone	73	1.35	0.76	-0.59	0.84	-2.80	-0.50	2.20	69	1.27	1.18	-0.09	0.89	-3.80	0.00	2.60
SHBG (ug/dl)	73	1.48	4.61	3.13	2.30	-2.30	3.10	10.70	69	1.46	1.59	0.13	0.63	-1.60	0.10	3.00
DHEAS (ug/dl)	72	184.15	128.79	-55.36	50.21	-229.00	-55.00	52.00	69	166.26	168.67	2.41	46.91	-143.00	2.00	100.00

SHBG - Sex hormone binding globulin
DHEAS - Dehydroepiandosterone sulfate

Table 22. Correlation Between Hormones and Lesion Counts

	ORTHO TRI-CYCLEN					Placebo				
r*	Change of Testosterone	Change of Free Testosterone	Change of % Free Testosterone	Change of SHBG	Change of DHEAS	Change of Testosterone	Change of Free Testosterone	Change of % Free Testosterone	Change of SHBG	Change of DHEAS
Change of Total Lesions	-0.02657 0.8234 73	0.23655 0.0439 73	0.08864 0.4558 73	-0.17581 0.1368 73	0.15297 0.1995 72	-0.07708 0.5290 69	0.00360 0.9766 69	0.00848 0.9448 69	-0.04524 0.7121 69	0.07533 0.5384 69
Change of Inflammatory Lesions	0.07793 0.5123 73	0.36023 0.0017 73	0.12079 0.3087 73	-0.17376 0.1415 73	0.14825 0.2139 72	0.08967 0.4637 69	0.07315 0.5503 69	0.02406 0.8444 69	0.02092 0.8645 69	-0.02701 0.8256 69
Change of Total Comedones	-0.07884 0.5073 73	0.10782 0.3639 73	0.04840 0.6843 73	-0.13310 0.2616 73	0.11724 0.3267 72	-0.11869 0.3314 69	-0.02582 0.8332 69	-0.00069 0.9955 69	-0.05680 0.6429 69	0.09130 0.4556 69
Change of Open Comedones	-0.06224 0.6009 73	0.08022 0.4999 73	0.03674 0.7577 73	-0.00303 0.9797 73	0.01765 0.8830 72	-0.05904 0.6299 69	0.02523 0.8369 69	0.08708 0.4768 69	0.02163 0.8600 69	0.11294 0.3555 69
Change of Closed Comedones	-0.03056 0.7974 73	0.04767 0.6888 73	0.02052 0.8632 73	-0.17407 0.1408 73	0.13465 0.2595 72	-0.11433 0.3496 69	-0.06577 0.5913 69	-0.09458 0.4395 69	-0.10830 0.3757 69	0.01600 0.8962 69
Change of Papules	0.11206 0.3452 73	0.35477 0.0021 73	0.12250 0.3018 73	-0.14639 0.2165 73	0.12761 0.2854 72	0.15225 0.2117 69	0.12796 0.2947 69	0.03504 0.7750 69	0.04643 0.7048 69	0.04290 0.7263 69
Change of Pustules	-0.03707 0.7555 73	0.07077 0.5519 73	0.03389 0.7759 73	-0.04002 0.7368 73	0.07945 0.5071 72	-0.10159 0.4062 69	-0.09504 0.4373 69	-0.02798 0.8195 69	-0.01013 0.9342 69	-0.10568 0.3875 69
Change of Nodules	-0.24691 0.0352 73	-0.06630 0.5773 73	-0.10967 0.3557 73	-0.25920 0.0268 73	0.00506 0.9664 72	0.01508 0.9021 69	0.03238 0.7917 69	0.05850 0.6331 69	-0.15206 0.2123 69	-0.19342 0.1113 69

Reviewer's Comments: Except for a slight increased baseline DHEAS detected in the placebo group; the treatment groups had similar baseline laboratory values. Significantly decreased free testosterone ($p = 0.001$), total testosterone ($p = 0.001$) and DHEAS ($p = 0.001$) were observed at the last evaluable visit for the ORTHO TRI-CYCLEN treated patients. A significant correlation was found between the decrease in inflammatory lesions and free testosterone ($p = 0.0017$); similarly, a significant correlation was found between papules and free testosterone ($p = 0.0439$).

Assessment Efficacy of Study N93-034

Reviewer's Comments: The study design for this protocol was adequate to assess the efficacy of ORTHO TRI-CYCLEN in the treatment of female patients with moderately severe acne vulgaris; the investigators were well qualified. Analysis of lesion counts suggests that greater resolution of papular as opposed to comedonal lesions occurs. This result is not surprising; patients with comedonal lesions tend to respond to topical comedolytic agents and are less likely to be treated with systemic drugs. The patient and investigator assessments were consistent in grading ORTHO TRI-CYCLEN as statistically better than placebo in overall improvement of acne.

The additional information obtained from the hormonal evaluation is supportive of the clinical subjective data, suggesting that the papular form of acne may be androgen sensitive.

The results of this study support the efficacy of ORTHO TRI-CYCLEN in the treatment of moderately severe acne vulgaris in female patients.

Study N93-035 A Double-Blind, Multicenter, Placebo-Controlled Study Evaluating the Efficacy of ORTHO TRI-CYCLEN in the Treatment of Moderate Acne Vulgaris.

This randomized, double-blind placebo controlled study designed to assess the efficacy and safety of ORTHO TRI-CYCLEN in the treatment of female patients with moderately severe acne vulgaris followed the same conduct as Study N93-034 excluding the hormonal assessment. Two-hundred thirty-one patients were evaluable for safety; 110 of whom were randomized to the ORTHO TRI-CYCLEN group; 121 were randomized to the placebo group.

One-hundred seventy-two patients completed the study: 82 in the ORTHO TRI-CYCLEN group and 90 in the placebo group. Fifty-eight patients discontinued: 28 (25.5%) of whom were in the ORTHO TRI-CYCLEN group and 30 (24.8%) of whom were in the placebo group. Note: One additional patient in the placebo group, listed as continuing in the study did complete a final visit after the database freeze date.

Eleven of the premature discontinuations were for an adverse event. One subject in each treatment group terminated because of an exacerbation of acne; an additional 5 or (4.5%) of the ORTHO TRI-CYCLEN group and 4 (3.3%) in the placebo group terminated for non-serious adverse events such as: nausea, abdominal pain, weight gain, depression and headache. There were no significant differences in the type or severity of event that related to either treatment group (Table 23).

Table 23. Disposition of Subjects

		Treatment				Total	
		ORTHO TRI-CYCLEN		Placebo			
		N	%	N	%	N	%
Number of Subjects Exposed		110	100.0	121	100.0	231	100.0
Total Completed		82	74.5	90	74.4	172	74.5
Total Discontinued		28	25.5	30	24.8	58	25.1
Total Continuing on Study		0	0	1	0.8	1	0.4
Reason for Early Termination	Adverse Event	5	4.5	4	3.3	9	3.9
	Significant Exacerbation of Acne	1	0.9	1	0.8	2	0.9
	Significant Protocol Violation	2	1.8	7	5.8	9	3.9
	Subject's Request	6	5.5	3	2.5	9	3.9
	Intercurrent Illness	1	0.9	2	1.7	3	1.3
	Lost to Follow-up	10	9.1	8	6.6	18	7.8
	Other	3	2.7	5	4.1	8	3.5

Study N93-035 Demographics Cont'd

Two-hundred fifty-seven female patients aged 15 to 49 years were randomized into one of two treatment groups in this study. Demographics were assessed for the 231 evaluable for safety patient group (Tables 24 and 25).

Table 24. Demographics - Age and Ethnic Group

Demographic Characteristics			Treatment		
			ORTHO TRI-CYCLEN	Placebo	TOTAL
Age at Enrollment (years)		N	118	113	231
		Mean	28.36	28.42	28.39
		SD	8.04	7.40	7.72
		Minimum	15	15	15
		Median	26.36	28.27	27.23
		Maximum	49	47	49
Ethnic Origin	Caucasian	N	99	89	188
		%	83.9	78.8	81.4
	Black	N	13	16	29
		%	11.0	14.2	12.6
	Oriental	N	2	3	5
		%	1.7	2.7	2.2
	Hispanic	N	4	5	9
		%	3.4	4.4	3.9
	Other	N	0	0	0
		%	0	0	0

Table 25. Demographics - Age Onset of Acne and Weight in Pounds

Demographic Characteristics		Treatment		
		ORTHO TRI-CYCLEN	Placebo	TOTAL
Age at Onset of Acne (years)	N	109	121	230
	Mean	14.57	15.28	14.94
	SD	4.48	5.86	5.25
	Minimum	8	8	8
	Median	13.00	13.00	13.00
	Maximum	32	45	45
Weight (lbs)	N	110	121	231
	Mean	144.20	149.64	147.05
	SD	30.29	37.49	34.29
	Minimum	105	85	85
	Median	135.00	139.00	138.00
	Maximum	255	253	255

Reviewer's Comments: The patients were demographically balanced between the two treatment groups relative to age, race and duration of disease.

Study N93-035 Cont'd

Efficacy analyses were performed on: 1) the intent-to-treat population (228 patients who took the study medication and had at least one ~~on~~ therapy efficacy assessment) and 2) the evaluable population (160 patients who completed the study and did not have major protocol variations) (Table 26). Efficacy parameters were the same as in Study N93-034.

Table 26. Intent-to-Treat and Evaluable Patients for Efficacy

Subject Evaluability		Treatment				Total	
		ORTHO TRI-CYCLEN		Placebo			
		N	%	N	%	N	%
Evaluable		79	73.8	81	66.9	160	70.2
Non-Evaluable		28	26.2	40	33.1	68	29.8
Reason Non-Evaluable	Did Not Complete Study	25	23.4	31*	25.6	56	24.6
	Non-Allowed Concurrent Medication During Study	3	2.8	8	6.6	11	4.8
	Inadequate Lesion Count at Enrollment	0	0.0	0	0.0	0	0.0
	Non-Allowed Concurrent Medication Use During Study; Inadequate Washout of Pre-Study Medications	0	0.0	1	0.8	1	0.4
Total		107	100.0	121	100.0	228	100.0

Reviewer's Comments: As in Study N93-034, the numbers and percentages of patients who were evaluable-for-efficacy and who constituted the intent-to-treat populations were equal between the two groups.

Study N93-035 Cont'd

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Results Primary Efficacy Variables Study N93-035:

Table 27. Change in Inflammatory Lesion Count from Baseline

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	19.50	9.85	9.64	10.70	-34.00	9.00	37.00	107	50.17	48.54	-216.67	63.64	100.00
	Placebo	121	19.31	13.52	5.79	10.84	-37.00	7.00	40.00	121	29.04	59.80	-290.00	45.00	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	19.42	7.66	11.76	8.90	-20.00	11.00	37.00	79	62.00	30.29	-43.48	70.37	100.00
	Placebo	81	20.01	12.42	7.59	8.94	-18.00	8.00	40.00	81	38.61	41.15	-72.00	50.00	92.31

Reviewer's Comments: The mean change in inflammatory lesion counts decreased significantly in the ORTHO TRI-CYCLEN treated group as compared to the placebo group; p-values for the intent-to-treat and evaluable patients were consistent ($p = 0.0036$ and $p = 0.001$ respectively).

Table 28. Change in Total Lesion Count from Baseline

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	53.78	30.47	23.31	26.16	-90.00	22.00	97.00	107	43.93	37.81	-102.44	51.85	96.23
	Placebo	121	51.05	39.14	11.91	23.72	-67.00	14.00	85.00	121	23.10	47.69	-219.23	33.01	91.80
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	54.75	25.65	29.10	22.79	-26.00	25.00	97.00	79	53.05	29.91	-52.00	59.70	96.23
	Placebo	81	49.96	35.88	14.09	23.58	-67.00	15.00	85.00	81	26.78	43.67	-125.00	35.71	91.80

Reviewer's Comments: Mean decreases in the ORTHO TRI-CYCLEN group were significantly greater than those in the placebo treated groups for the total lesion count (p value = 0.0004). These results correlate well with those in Table 27.

Results Primary Efficacy Variables Study N93-035 Cont'd

Table 29. Investigator's Global Assessment Intent-to-Treat

Global Progress of Treatment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Excellent	31	29.0	18	14.9
	Good	34	31.8	32	26.4
	Fair	24	22.4	28	23.1
	Subtotal	89	83.2	78	64.5
Not Improved	No Change	13	12.1	27	22.3
	Worse	5	4.7	16	13.2
	Subtotal	18	16.8	43	35.5
Total		107	100.0	121	100.0

Reviewers Comments: The investigator's assessment demonstrated that 83.2% of ORTHO TRI-CYCLEN treated patients improved as compared to 64.5% of placebo treated patients, the statistical significance of which provided a p value of 0.001 favoring ORTHO TRI-CYCLEN. Twenty-nine percent of the ORTHO TRI-CYCLEN group was rated as excellent as opposed to 14.9% of the placebo group. Seventeen percent of the ORTHO TRI-CYCLEN treated patients were described as worse; 35.5 percent of the placebo group received the same designation.

Table 30. Investigator's Global Assessment Evaluable-for-Efficacy

Global Progress of Treatment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Excellent	30	38.0	15	18.5
	Good	28	35.4	24	29.6
	Fair	16	20.3	14	17.3
	Subtotal	74	93.7	53	65.4
Not Improved	No Change	3	3.8	20	24.7
	Worse	2	2.5	8	9.9
	Subtotal	5	6.3	28	34.6
Total		79	100.0	81	100.0

Reviewer's Comments: As with the intent-to-treat group; improvement in the evaluable-for-efficacy group was noted to be statistically greater in the ORTHO TRI-CYCLEN treated patients than in the placebo group ($p<0.001$). Six percent of ORTHO TRI-CYCLEN patients were rated as worse versus 35.5% of placebo patients.

Results Secondary Efficacy Variables N93-035 Cont'd

Subject's End of Therapy Self-Assessment of Acne Improvement

Table 31a) Intent-to-Treat

Subject Self-Assessment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Much Improved	36	38.3	24	22.4
	Somewhat Improved	42	44.7	51	47.7
	Subtotal	78	83.0	75	70.1
Not Improved	Not Improved	11	11.7	24	22.4
	Worse	4	4.3	7	6.5
	Much Worse	1	1.1	1	0.9
	Subtotal	16	17.0	32	29.9
Total		94	100.0	107	100.0

Table 31b) Evaluable-for-Efficacy

Subject Self-Assessment		Treatment			
		ORTHO TRI-CYCLEN		Placebo	
		N	%	N	%
Improved	Much Improved	34	43.0	18	22.2
	Somewhat Improved	39	49.4	40	49.4
	Subtotal	73	92.4	58	71.6
Not Improved	Not Improved	5	6.3	19	23.5
	Worse	1	1.3	4	4.9
	Much Worse	0		0	
	Subtotal	6	7.6	23	28.4
Total		79	100.0	81	100.0

Reviewer's Comments: Both the intent-to-treat and the evaluable-for-efficacy results from the patient's self assessment for acne improvement were statistically in favor of ORTHO TRI-CYCLEN over placebo ($p = 0.025$ and $p < 0.001$, respectively).

Subject's Comparison to Prior Acne Treatment at Study Termination

Table 32a) Intent-to-Treat

Comparison to Prior Acne Treatment	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
Better	48	51.1	40	37.4
The Same	27	28.7	32	29.9
Worse	9	9.6	23	21.5
Not Applicable	10	10.6	12	11.2
TOTAL	94	100.0	107	100.0

Table 32b) Evaluble for Efficacy

Comparison to Prior Acne Treatment	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
Better	45	57.0	29	35.8
The Same	22	27.8	24	29.6
Worse	4	5.1	19	23.5
Not Applicable	8	10.1	9	11.1
TOTAL	79	100.0	81	100.0

Reviewer's Comments: The results of the intent-to-treat group comparison did not demonstrate statistical significance ($p = 0.079$). On the other hand, the evaluable-for-efficacy patients who received ORTHO TRI-CYCLEN felt that it was better than other anti-acne therapies to a statistically significant degree ($p = 0.006$)

Results Secondary Efficacy Variables P93-035 Cont'd

Table 33. Subject's Desire to Continue Study Treatment at Study Termination
Intent-to-Treat

Would Subject Continue ORTHO TRI-CYCLEN?	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
No	24	25.5	39	36.4
Yes	70	74.5	68	63.6
TOTAL	94	100.0	107	100.0

Table 34. Subject's Desire to Continue Study Treatment at Study Termination
Evaluable-for-Efficacy

Would Subject Continue ORTHO TRI-CYCLEN?	Treatment			
	ORTHO TRI-CYCLEN		Placebo	
	N	%	N	%
No	15	19.0	28	34.6
Yes	64	81.0	53	65.4
TOTAL	79	100.0	81	100.0

Reviewer's Comments: Analysis of the data from the two groups (intent-to-treat and evaluable-for-efficacy) provide differing results: the number and percentage of ORTHO TRI-CYCLEN treated patients who were willing to continue therapy was 70 and 74.5% compared to 68 and 63.6% of the placebo group ($p = 0.070$), respectively. Sixty-four patients (81%) of the evaluable-for-efficacy patients expressed a desire to continue treatment with ORTHO TRI-CYCLEN as opposed to 53 (65.4%) of the placebo group ($p = 0.019$).

Results Secondary Efficacy Variables P93-035 Cont'd

Table 35. Within Cycle Analysis of Inflammatory and Total Lesions
Intent-to-Treat

Lesion Count	Treatment	N	Baseline Mean	Mean (Cycle 6, Week 1)	Mean (Cycle 6, Week 2)	Mean (Cycle 6, Week 3)	P-value for Hotelling's T^2 Test
Inflammatory Lesions	ORTHO TRI-CYCLEN	72	19.69	8.42	7.83	8.08	0.6098
	Placebo	78	19.79	13.58	12.67	13.69	0.1851
Total Lesions	ORTHO TRI-CYCLEN	72	54.64	28.28	25.54	27.43	0.0744
	Placebo	78	51.60	36.37	36.22	39.36	0.0858
Total Comedones	ORTHO TRI-CYCLEN	72	34.94	19.86	17.71	19.35	0.1209
	Placebo	78	31.81	22.79	23.55	25.67	0.0942

Table 36. Within Cycle Analysis of Inflammatory and Total Lesions
Evaluable-for-Efficacy

Lesion Count	Treatment	N	Baseline Mean	Mean (Cycle 6, Week 1)	Mean (Cycle 6, Week 2)	Mean (Cycle 6, Week 3)	P-value for Hotelling's T^2 Test
Inflammatory Lesions	ORTHO TRI-CYCLEN	69	19.94	8.39	7.97	8.26	0.7124
	Placebo	69	20.38	12.90	12.36	13.30	0.3323
Total Lesions	ORTHO TRI-CYCLEN	69	55.48	28.17	25.70	27.55	0.1158
	Placebo	69	51.33	34.71	35.09	38.46	0.0512
Total Comedones	ORTHO TRI-CYCLEN	69	35.54	19.78	17.72	19.29	0.1632
	Placebo	69	30.96	21.81	22.72	25.16	0.0562

Reviewer's Comments: There were no statistically significant within cycle differences demonstrated in the intent-to-treat or evaluable-for-efficacy groups favoring either therapy.

Results Secondary Efficacy Parameters N93-035 Cont'd

Table 37. Mean Change Open Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	9.65	5.41	4.24	9.74	-23.00	1.00	34.00	67	35.57	124.97	-800.00	75.00	100.00
	Placebo	121	12.44	8.42	4.02	13.49	-56.00	1.00	60.00	92	30.33	84.88	-400.00	47.06	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	9.78	4.18	5.61	10.05	-19.00	2.00	34.00	52	55.62	63.66	-200.00	77.50	100.00
	Placebo	81	10.16	7.40	2.77	13.28	-56.00	0.00	50.00	55	28.92	100.83	-400.00	54.84	100.00

Table 38. Mean Change Closed Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	24.63	15.21	9.42	16.54	-41.00	8.00	59.00	99	25.38	69.17	-266.67	46.43	100.00
	Placebo	121	19.31	17.20	2.11	14.12	-37.00	1.00	49.00	108	-7.10	94.08	-460.00	19.62	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	25.54	13.81	11.73	16.37	-27.00	9.00	59.00	73	31.66	69.47	-266.67	47.06	100.00
	Placebo	81	19.79	16.06	3.73	14.30	-37.00	1.00	49.00	72	-2.15	91.39	-460.00	18.26	100.00

Table 39. Mean Change Total Comedones

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	34.28	20.62	13.66	20.30	-64.00	9.00	81.00	107	35.65	54.86	-328.57	45.71	100.00
	Placebo	121	31.74	25.62	6.12	18.17	-61.00	6.00	67.00	121	12.21	62.07	-230.00	26.67	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	35.33	17.99	17.34	19.27	-46.00	14.00	81.00	79	43.17	55.34	-328.57	53.49	100.00
	Placebo	81	29.95	23.46	6.49	18.88	-61.00	6.00	67.00	81	13.55	64.67	-230.00	23.53	100.00

Reviewer's Comments: In the intent-to-treat and evaluable-for-efficacy populations there was a decrease in the mean number of total comedones and closed comedones in both treatment groups. ORTHO TRI-CYCLEN was statistically better than placebo with a p-value of 0.0050 and 0.0056 for closed comedones, respectively. Equally good results were obtained in the decreased mean number of total comedones (p-value 0.0022 and 0.003) for the intent-to-treat and evaluable-for-efficacy groups, respectively. A significant advantage was demonstrated in the evaluable-for-efficacy population ($p = 0.0007$) for ORTHO TRI-CYCLEN for the reduction in open comedones.

Results Secondary Efficacy Parameters N93-035 Cont'd

Table 40. Mean Change for Papules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	16.76	8.64	8.11	9.10	-26.00	8.00	36.00	107	39.68	98.33	-766.67	60.00	100.00
	Placebo	121	16.61	11.38	5.23	9.73	-35.00	7.00	34.00	121	26.64	62.15	-250.00	46.67	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	16.58	6.81	9.77	7.77	-19.00	9.00	36.00	79	59.70	32.89	-66.67	66.67	100.00
	Placebo	81	17.15	10.65	6.49	8.13	-14.00	7.00	34.00	81	35.01	45.56	-100.00	47.06	92.31

Table 41. Mean Change for Pustules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	2.49	1.06	1.43	3.25	-7.00	0.00	12.00	57	56.31	101.92	-600.00	100.00	100.00
	Placebo	121	2.23	1.64	0.59	3.59	-18.00	0.00	13.00	67	38.71	113.72	-500.00	83.33	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	2.53	0.68	1.85	3.07	-2.00	0.00	12.00	41	76.87	36.86	-66.67	100.00	100.00
	Placebo	81	2.46	1.36	1.10	3.15	-8.00	0.00	13.00	44	53.30	99.10	-400.00	100.00	100.00

Table 42. Mean Change for Nodules

Population	Treatment	N for Change	Baseline Mean	Last Available Visit Mean	Mean Change	SD Change	Minimum Change	Median Change	Maximum Change	N for % Change	Mean % Change	SD % Change	Minimum % Change	Median % Change	Maximum % Change
Intent-to-Treat	ORTHO TRI-CYCLEN	107	0.25	0.15	0.10	0.71	-3.00	0.00	2.00	19	90.35	25.65	0.00	100.00	100.00
	Placebo	121	0.46	0.50	-0.03	1.13	-5.00	0.00	3.00	34	41.67	86.48	-200.00	100.00	100.00
Subjects Evaluable for Efficacy	ORTHO TRI-CYCLEN	79	0.30	0.16	0.14	0.76	-3.00	0.00	2.00	16	88.54	27.70	0.00	100.00	100.00
	Placebo	81	0.41	0.41	0.00	1.06	-5.00	0.00	3.00	19	48.77	83.17	-200.00	100.00	100.00

Reviewer's Comments: With the exception of the intent-to-treat group analysis of pustules, all results demonstrated statistical significance favoring ORTHO TRI-CYCLEN over placebo. P values were 0.0104 and 0.0005 for papules, 0.0675 and 0.0191 for pustules, and 0.0141 and 0.586 for nodules (representing the intent-to-treat and evaluable-for-efficacy populations, respectively).

Assessment Efficacy Results Study N93-035

Reviewer's Comments: The overall results of study N93-035 are consistent with those obtained in Study N93-034. A statistically significant number of ORTHO TRI-CYCLEN treated patients had a decrease in the number of acne lesions and were improved according to the assessments of both the patients and the investigators. There were minor differences in the results, reflected in the number of lesion types (comedones/open or closed) which improved to a greater degree. Overall the number of comedones decreased significantly. This study is supportive of the efficacy of ORTHO TRI-CYCLEN in the treatment of moderately severe acne vulgaris.

Safety Results

Adverse events - Safety was evaluated by the recording of adverse events during the study conduct. No laboratory was data obtained. Results are listed in the following table for both studies as ORTHO TRI-CYCLEN is not a new drug. Treatment of acne vulgaris is a new indication. The adverse events occurring in the studies, therefore, can be combined and assessed according to the benefit/risk ratio.

Table 43. Incidence of Adverse Events by Organ System

System Organ Class	N93-034				N93-035				Combined			
	ORTHO TRI CYCLEN		Placebo		ORTHO TRI CYCLEN		Placebo		ORTHO TRI CYCLEN		Placebo	
	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL	118	100.0	113	100.0	110	100.0	121	100.0	228	100.0	234	100.0
Any AE	102	86.4	94	83.2	79	71.8	77	63.6	181	79.4	171	73.1
No WHO Preferred Term Available*	0	0.0	0	0.0	2	1.8	0	0.0	2	0.9	0	0.0
SKIN*AND APPENDAGES DISORDERS	10	8.5	8	7.1	9	8.2	9	7.4	19	8.3	17	7.3
MUSCULO-SKELETAL SYSTEM DISORDERS	8	6.8	13	11.5	4	3.6	4	3.3	12	5.3	17	7.3
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	34	28.8	39	34.5	12	10.9	14	11.6	46	20.2	53	22.7
VISION DISORDERS	0	0.0	1	0.9	2	1.8	3	2.5	2	0.9	4	1.7
HEARING AND VESTIBULAR DISORDERS	0	0.0	0	0.0	1	0.9	1	0.8	1	0.4	1	0.4
PSYCHIATRIC DISORDERS	11	9.3	9	8.0	6	5.5	4	3.3	17	7.5	13	5.6
GASTRO-INTESTINAL SYSTEM DISORDERS	39	33.1	31	27.4	26	23.6	16	13.2	65	28.5	47	20.1
METABOLIC AND NUTRITIONAL DISORDERS	4	3.4	5	4.4	4	3.6	1	0.8	8	3.5	6	2.6
CARDIOVASCULAR DISORDERS, GENERAL	1	0.9	1	0.9	1	0.9	1	0.8	2	0.9	2	0.9
HEART RATE AND RHYTHM DISORDERS	0	0.0	1	0.9	0	0.0	0	0.0	0	0.0	1	0.4
VASCULAR (EXTRACARDIAC) DISORDERS	0	0.0	0	0.0	1	0.9	0	0.0	1	0.4	0	0.0
RESPIRATORY SYSTEM DISORDERS	38	32.2	44	38.9	30	27.3	21	17.4	68	29.8	65	27.8
RED BLOOD CELL DISORDERS	0	0.0	0	0.0	1	0.9	0	0.0	1	0.4	0	0.0
WHITE CELL AND RES DISORDERS	0	0.0	0	0.0	0	0.0	2	1.7	0	0.0	2	0.9
PLATELET,BLEEDING & CLOTTING DISORDERS	1	0.9	1	0.9	0	0.0	0	0.0	1	0.4	1	0.4
URINARY SYSTEM DISORDERS	6	5.1	4	3.5	1	0.9	4	3.3	7	3.1	8	3.4
REPRODUCTIVE DISORDERS, FEMALE	50	42.4	28	24.8	26	23.6	24	19.8	76	33.3	52	22.2
NEOPLASM	2	1.7	0	0.0	0	0.0	1	0.8	2	0.9	1	0.4
BODY AS A WHOLE - GENERAL DISORDERS	36	30.5	24	21.2	16	14.6	19	15.7	52	22.8	43	18.4
APPLICATION SITE DISORDERS	0	0.0	1	0.9	1	0.9	0	0.0	1	0.4	1	0.4

Assessment Safety

Reviewer's Comments: The incidence of adverse events was equal in both groups with 3 exceptions. There were greater numbers of events occurring in the reproductive system in ORTHO TRI-CYCLEN treated patients in Study N93-034 (50 [42%] vs 28 [25%]). There were greater numbers of ORTHO TRI-CYCLEN treated patients vs placebo treated patients who experienced gastro-intestinal disorders (55 [29%] vs 47 [21%]) in Study N93-035. There was a slight increase in "body as a whole" events for ORTHO TRI-CYCLEN treated patients in the studies combined (52 [23%] vs 43 [18%]). These results are anticipated based on the known adverse event profile of ORTHO TRI-CYCLEN. There were no serious advents reported directly related to study drug.

Commentary: The introduction of hormonal agents into the anti-acne treatment armamentarium represents a significant advance. It has long been theorized that hormonal manipulation may be beneficial for some sufferers of acne. The studies submitted in support of this NDA represent the first objective data which answers the question.

Conclusion: The studies submitted demonstrate that ORTHO TRI-CYCLEN is beneficical in treating acne in female patients with moderately active disease. The benefit/risk ratio suggests that treatment can be effective with a minimum of side effects.

Recommendation: ORTHO TRI-CYCLEN is approvable for the treatment of moderately severe acne vulgaris in females.

Medical Officer,

Ella L. Toombs, MD

Ella L. Toombs

cc: J M Katz, MD 11/6/96.
HFD-540/CSO/White
HFD-540/CHEM/Pappas
HFD-540/STAT/Srinivasan
HFD-540/BIO/Bashaw
HFD-540/Div Dir/Wilkin
HFD-540/Dep Dir/Katz

JW 11/15/96 As above with the following addition. Although the risk of taking oral contraceptives compares favorably with the risks inherent in pregnancy, acne vulgaris poses no such risks. Thus, oral contraceptive therapy for acne should be reserved for women whose acne cannot be controlled with topical acne therapy. The youngest patients were 15 years old.

Medical Officer's Review of Label NDA 20,681

Attached is a copy of the Physician's and Patient's Package Insert as submitted by the sponsor with revisions suggested by the reviewer. The information contained therein is a replica of the labeling used by the sponsor for the oral contraceptive indication for ORTHO TRI-CYCLEN with the addition of appropiately worded inclusions referring to the indication '. These inclusions are shaded and can be found in the following sections:

Clinical Pharmacology - Page 2

Indications and Usage - Page 3

Dosage and Administration - Page 22

Patient Package Insert - Page 28

Reviewer's Comments: The label as submitted by the sponsor is adequate and acceptable. At the suggestion of Dr. Linda Katz, the sponsor may want to include a "Clinical Studies" section which would contain the clinical trials data which is currently described under the "Indications and Usage" section on pages 4 - 6.

Ella L. Toombs, MD
Medical Officer

11/8/96

cc:
HFD-540/CSO/White
HFD-540/CHEM/Pappas
HFD-540/STAT/Srinivasan
HFD-540/BIO/Bashaw
HFD-540/DivDir/Wilkin
HFD-540/DepDir/Katz
HFD-540/MO/Toombs

11/19/96 As above with limits to age (≥ 15 years old) and achievement of menarche.

Clinical/Statistical Review and Evaluation

AUG 28 1996

NDA #/Drug Class	20-681/6S
Applicant:	R.W. Johnson Pharmaceutical Research Institute
Name of the Drug:	Ortho-Tricyclen^{R} (norgestimate/ethinyl estradiol)
Documents to be reviewed:	CANDA installed by the sponsor
Indication:	Moderate Acne Vulgaris
Type of Report:	Clinical/Statistical
Clinical Input:	Ella Toombs, M.D. (HFD-540)

I. Introduction:

Two Phase III pivotal trials were conducted by the sponsor in the United States to evaluate the efficacy of the commercially-marketed multiphasic combination oral contraceptive ORTHO TRI-CYCLEN^{R} (norgetimate/ethinyl estradiol) for the treatment of moderate acne vulgaris in ***females***. These two studies were multicenter, double-blind, randomized, placebo-controlled clinical trials designed to evaluate the efficacy of ORTHO-TRICYCLEN for this indication. The safety of ORTHO-TRYCYCLEN in healthy females has been established and documented in previous clinical trials as well as in marketed use as a contraceptive. Inclusion/exclusion criteria were written to obtain enrollment of healthy, female subjects with moderate acne vulgaris, no known contraindications to oral contraceptive therapy, and no concomitant medical conditions or therapies that would pose any potential risk for participating subjects or interfere with safety or efficacy assessments. The primary efficacy variables were as follows:

- Change in ***inflammatory*** lesion count (papules + pustules + nodules) from baseline to the last available evaluation;

- Change in ***total*** lesion count (comedones (open and closed) + papules + pustules + nodules) from baseline to the last available evaluation; and,

- ***Percentage of subjects showing improvement*** ("fair," "good," or "excellent" progress versus "no change" or "worse") on the investigator's global assessment.

According to the reviewing medical officer, the sponsor has to show superiority of ORTHO-TRICYCLEN over placebo, relative to ***inflammatory and total lesions and percentage of subjects showing improvement*** and so no adjustment was made for multiple comparisons. No interim analysis was planned.

II. Review of Studies

1. Study N93-034

a. Study design

This Phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of ORTHO-TRICYCLEN in the treatment of moderate acne vulgaris. Twelve study sites in the United States enrolled subjects in this study; the number of subjects randomized to study drug/placebo per center ranged from 5 to 48. Subjects were females 15 to 49 years of age in good general health; with moderate acne vulgaris (Grade II or III); with no contraindications to oral contraceptives (OCS), and who were willing to take OCS.

Subjects were randomly assigned to either active or color-matched placebo treatment under double-blind conditions. They were evaluated over a period of 6 months, with follow-up visits scheduled during specific times of the subjects' menstrual cycles, for a total of 9 scheduled visits: pre-study/admission test (Visit 1), one visit during each of Cycles 1 through 5 (Visits 2 through 6 during days 17 to 24 of the cycle), and three visits during Cycle 6 (Visits 7 through 9 during cycle days 1 to 7, 8 to 14, and 17 to 24, respectively).

Each DIALPAK Tablet Dispenser provided a one month course (28 days) of treatment. Each month, active dose subjects received 3 consecutive weeks of active treatment (I.e., tablets containing fixed dose of ethinyl estradiol and increasing doses or norgestimate), followed by inactive drug during the last week. Placebo-dosed subjects received color-matched tablets. Compliance to the treatment regimen and use of concurrent medications was assessed at each monthly visit during the dosing period by counting the remaining tablets in the returned used packages, and by interviewing subjects.

Efficacy was assessed on facial lesion counts (performed during Visits 1 through 9),a clinical assessment of lesions as compared to baseline(performed during Visits 2 through 8), and an investigator global assessment (performed at Visit 9, or at the early termination visit). In all subjects at six selected sites, baseline and termination assessment of certain hormonal parameters (total testosterone, free testosterone, sex hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS)) were performed to assess the clinical usefulness of these measurements as predictors of both acne severity and subject responsiveness to treatment.

Safety was assessed throughout the dosing period on the incidence and severity of adverse events. Information on adverse events was collected through interviews with the subjects.

b. Study Population

A total of 244 subjects, 122 per treatment group, were expected to be enrolled in the trial. For inclusion/exclusion criteria, please refer to reviewing medical officer's review. Subjects were randomly assigned to either active or placebo treatment under double-blind conditions.

Subjects were evaluated over a period of 6 months, with follow-up visits scheduled during specific times of the subjects' menstrual cycles, for a total of 9 scheduled visits: pre-study/admission visit (Visit 1), one visit during each of Cycles 1 through 5 (Visits 2 through 6), and three visits during Cycle 6 (Visits 7 through 9).

c. Efficacy and Safety Evaluations:

The following assessments were performed on Visits 2 through 8: facial lesion count and investigator rating of the subject's progress with treatment as compared to baseline. Subjects who missed 3 or more active doses in 2 or more consecutive cycles were discontinued from the study. At the termination visit (Visit 9) or at the time of early discontinuation, the following assessments were performed: clinical assessment and facial lesion count; hormonal assessments at selected investigational centers (including total testosterone, free testosterone, SHBG, and DHEAS); urine pregnancy test; investigator global assessment rating; end-of-therapy self-assessment questionnaire (completed by subjects); adverse events; use of concurrent therapy or topical products; and missed doses of study drug.

Efficacy of the study was assessed on the following ***primary efficacy parameters***: (1) Change in inflammatory lesion count (papules + pustules + nodules) from baseline to the last available evaluation; (2) Change in total lesion count (comedones (open and closed) + papules + pustules + nodules) from baseline to the last available evaluation; and (3) Percentage of subjects showing improvement ("fair," "good," or "excellent" progress versus "no change" or "worse") on the investigator's global assessment. Secondary efficacy parameters were, the percent of subjects showing improvement on rating of subject's progress of treatment at each visit, change and percent change in inflammatory and total lesion count from baseline to each scheduled evaluation, change and percent change in comdone (total, open, and closed), papule, pustule, and nodule counts from baseline to the last available and each scheduled evaluation, percentage distribution of subject responses from the end-of-therapy self-assessment questionnaire for acne improvement, comparison of ORTHO TRI-CYCLEN to prior acne treatments, and desire to continue ORTHO TRI-CYCLEN use("no or "yes") at study termination, change in hormone levels, including total testosterone, free testosterone, % free testosterone, SHBG, and DHEAS, from baseline to the last available evaluation and repeated measurements analysis of the difference in mean lesion counts at the three visits during Cycle 6.

Safety was assessed on the incidence and type of adverse events reported from Visit 2 through Visit 9. Relatedness of the study drug to the adverse event was recorded on CRFs as "certain," "probable/likely," "possible," and "unlikely" according to criteria outlined in the protocol.

d. Statistical Methods

The primary efficacy analyses were conducted as planned in the protocol. Efficacy analyses were performed on two data sets: (1) intent-to-treat; and (2) evaluable-for-efficacy. In addition to descriptive statistics, the statistical significance of the difference between treatment groups were assessed for the end-of-therapy self-assessment questionnaire using the Cochran-Mantel-Haenszel test, with center as the stratifying variable. Analysis of the hormonal parameters (total testosterone, free testosterone, SHBG, and DHEAS) was done using a simple correlation analysis to investigate the correlation between change in hormone levels from baseline to last available result. Further investigation was performed using a regression analysis.

For each treatment group, Hotelling's T^2 test was used for the repeated measurements analysis described in the protocol to test the hypothesis of no difference in mean lesion counts at the three visits during Cycle 6. Using the intent-to-treat population, analysis of covariance was performed at each cycle to determine the earliest cycle at which statistical significance occurred. This analysis was performed on inflammatory lesion count and total lesion count. All analyses were conducted at the 0.05 significance level except for those for interaction, which were conducted at the 0.10 significance level.

Large clinically meaningful differences between treatment groups were evaluated statistically using Chi-square or Fisher's Exact tests.

e. Efficacy results

1. Demographic and Baseline Characteristics

Table I summarizes the different data sets used in the analysis of the results.

Table I

Population	Treatment				Total	
	Ortho Tri-Cyclen		Placebo			
	N	%	N	%	N	%
All subjects Randomized	126	100.0	124	100.0	250	100.0
Subjects Evaluable for Safety	118	93.7	113	91.1	231	92.4
Intent-to-Treat	114	90.5	113	91.1	227	90.8
Subjects Evaluable for Efficacy	84	66.7	80	64.5	164	65.6

There were statistically no significant differences between the two treatment groups relative to age, race, past medical history, height blood pressure and smoking status ($p>0.05$). Subjects were also evaluated for comparability of efficacy parameters at baseline. The difference between treatment groups was not statistically significant for either lesion type.

Of the 231 subjects evaluable for safety, 118 were in the ORTHO TRI-CYCLEN group and 113 in the placebo group. A total of 179 subjects (77.5%) completed the study according to protocol specifications: 92 subjects (78.0%) in the ORTHO TRI-CYCLEN group and 87 subjects (77.0%) in the placebo group. There were no statistically significant differences between treatment groups regarding the study completion. A total of 52 subjects (22.5%) discontinued from the study prematurely: 26 subjects (22.0%) in the ORTHO TRI-CYCLEN group and 26 subjects (23.0%) in the placebo group.

Of the 52 subjects who terminated early, 22 subjects discontinued for either an adverse event or worsening of acne. A total of 18 (7.8%) early discontinuations were due to an adverse event: 13 subject (11.0%) in the ORTHO TRI-CYCLEN group and 5 subjects (4.4%) in the placebo group. In addition, 4 subjects in the ORTHO TRI-CYCLEN group discontinued due to a significant exacerbation of acne. These 4 subjects represent 3.4% of the subjects exposed to ORTHO TRI-CYCLEN. There were no discontinuations due to exacerbation of acne in the placebo group. Statistical evaluation by Cochran-Mantel-Haenszel test of this parameter was performed, and a

statistically significant difference (p = 0.038) was found between the treatment groups. The remaining 30 of 52 subjects discontinued for reasons such as, significant protocol violations, subject's request, lost to follow-up and other reasons. Most of the discontinuations occurred during the first half of the study; out of the 52 early terminations, 43 occurred during Cycles 1-3. The number of terminations in this time period was similar in both treatment group (23 in the ORTHO TRI-CYCLEN group and 20 in the placebo group).

The majority of the subjects took all of their pills according to the protocol-specified regimen. In the evaluable-for-safety population, the percentage of subjects who did not miss any pills within a given cycle ranged from 84.3% (97/115) to 93.2% (82/88) in the ORTHO TRI-CYCLE group and from 90.0% (99/110) to 97.8% (90/92) in the placebo group.

2. Efficacy Analyses

The efficacy analysis was performed both on the intent-to-treat population, defined in the protocol as the subjects who took study medication and who had at least one on-therapy efficacy assessment (227 subjects), and on the evaluable-for-efficacy population, defined as those subjects who completed the study and who did not have major protocol variations (inadequate lesion counts, disallowed concurrent medications, etc.) (164 subjects).

In addition, analyses of certain hormonal parameters were performed for all subjects in six selected investigational sites. As with the other efficacy parameters, the data from these sites were analyzed both for the intent-to-treat subjects (142 subjects from six sites) and for the subjects that were evaluable for efficacy (117 subjects from six sites). Primary efficacy measures included the change from baseline to last available evaluation for inflammatory lesions, total lesions, and investigator's global assessment.

In the intent-to-treat population, the mean ***inflammatory lesion count*** decreased from baseline to the last available result in both treatment groups. The mean change was statistically significantly greater (p = 0.0203) in the ORTHO TRI-CYCLEN group than in the placebo group: 9.3 vs 6.7 or a 45.4% decrease from baseline vs. 31.5%. The mean change ranged from -17 to 69 in the ORTHO TRI-CYCLEN group and from -40 to 71 in the placebo group. In the evaluable-for-efficacy population, the mean ***inflammatory lesion count*** also decreased from baseline to Cycle 6 in both treatment groups. As in the intent-to-treat population, the mean change was statistically significantly greater (p = 0.0096) in the ORTHO TRI-CYCLEN group (9.9; range -17 to 44) than in the placebo group (6.9; range -40 to 41). The mean percentage change was 51.4% and 34.6%, respectively.

In the intent-to-treat population, the mean ***total lesion count*** decreased from baseline to the last available result in both treatment groups. The mean change in total lesion count was greater in the ORTHO TRI-CYCLEN group than in the placebo group (19.3), and the difference approached statistical significance ($p=0.0762$). Overall, the mean percentage change was 39.5% in the ORTHO TRI-CYCLEN group and 31.9% in the placebo group. In the evaluable-for-efficacy population, the mean ***total lesion count*** decreased from baseline to Cycle 6 in both treatment groups. The mean change in total lesion count was statistically greater ($p=0.0007$) in the ORTHO TRI-CYCLEN group (27.8; range -29 to 106), than in the placebo group (19.1; range -45 to 105). The mean percentage change was 46.4% and 33.9%, respectively.

The investigators rated each subject on global improvement of facial acne lesions at the last visit. A total of 89 subjects (78.1%) in the ORTHO TRI-CYCLEN group were rated as "improved" as compared to 69 subjects (61.1%) in the placebo group. Conversely, 25 subjects (21.9%) in the ORTHO TRI-CYCLEN group showed no improvement at the end of study as compared to 44 subjects (38.9%) in the placebo group. The difference between treatment groups regarding the subjects who did improve versus those who did not improve was statistically significant ($p=0.004$). The improved category was comprised of "excellent," "good'" and "fair" and the no-improvement category included "no change" and "worse." Note that 26 subjects (22.8%) in the ORTHO TRI-CYCLEN group as compared to 8 subjects (7.1%) in the placebo group were rated "excellent." In contrast, only 13 subjects (11.4%) in the ORTHO TRI-CYCLEN group as compared to 36 subjects (31.9%) in the placebo group showed no change. 12 subjects (10.5%) in the ORTHO TRI-CYCLEN group and 8 subjects (7.1%) in the placebo group showed worsening of acne. The distribution of "good" and "fair" results were similar in both treatment groups. There was a significant difference between test groups based on the five point improvement category scale ($p<0.001$). Investigator's global assessment was also evaluated in the evaluable-for-efficacy subset. As in the intent-to-treat population, the difference between treatment groups was significant with respect to improved/not improved subjects ($p=0.001$). The distribution of "good" and "fair" results were similar in both treatment groups. The difference between treatment groups with respect to the five point improvement category scale was statistically significant ($p<0.001$) by Cochran Mantel Haenszel Test.

Secondary efficacy measures included each separate **lesion count** as well as ***subject's self-assessment at end of therapy and the change in hormone levels from pre-study to last available evaluation.*** ***Total comedones*** included both open and closed comedones. In the intent-to-treat population, the mean total comedone count decreased from baseline to the last available result in both treatment groups. The mean change in total comedones was greater in the ORTHO TRI-CYCLEN group (14.5) than in the placebo group (12.6), however, the difference between treatment groups was not statistically significant ($p=0.3072$). Comparing the adjusted mean for change

from baseline in the evaluable-for-efficacy population, treatment differences between treatment groups did reach statistical significance for total comedones (p = 0.0184).

In the intent-to-treat population, the mean ***open comedone*** count decreased from baseline to the last available visit in both treatment groups. Although the mean change was greater in the ORTHO TRI-CYCLEN group (8.1) than in the placebo group (6.3), the difference between treatment groups did not reach statistical significance (p = 0.9364). Comparing the adjusted mean for change from baseline in the evaluable-for-efficacy population, treatment differences were not statistically significant for open comedones (p = 0.7207).

In the intent-to-treat population, the mean change in ***closed comedones*** was 6.4 in both treatment groups. The difference between treatment groups was not statistically significant (p = 0.3043). In the evaluable-for -efficacy population, the mean change for closed comedones was statistically significantly greater (p = 0.0056) in the ORTHO TRI-CYCLE (10.3) group than in the placebo group (6.4).

In the intent-to-treat population, the mean change for ***papules*** was statistically significantly greater (p = 0.0218) in the ORTHO TRI-CYCLEN group (7.4) than in the placebo group (5.3). Treatment differences were also statistically significant (p = 0.0457) for papules in the evaluable-for-efficacy population.

In the intent-to-treat population, the mean change for ***pustules*** was slightly greater in the ORTHO TRI-CYCLEN group (1.8) than in the placebo group (1.3), however, this difference was not statistically significant. In the evaluable-for-efficacy population, statistically significant treatment differences were approached for pustules (p = 0.0693.

In the intent-to-treat population, the mean change in ***nodules*** was greater in the ORTHO TRI-CYCLEN group (0.13) than in the placebo group (0.04), however, the difference between treatment groups was not statistically significant (p = 0.0952). In the evaluable-for-efficacy population (164 subjects) the mean change was not significantly greater in the ORTHO TRI-CYCLEN GROUP (0.17) than in the placebo group (-0.04 (p = 0.1206).)

All subjects completed a ***self-assessment questionnaire*** at study termination. The questionnaires included a self-rating of acne improvement vs. no improvement at the end of therapy, a comparison of the study drug to prior acne treatment, and a yes/no question to determine the subject's desire to continue the study drug as a treatment for acne. In the intent-to-treat population, the difference between treatment groups was statistically significant for all three measures of the subject self-assessment (p < 0.047). In the evaluable-for-efficacy population, the differences between treatment groups were statistically significant for all three subject self-assessment

parameters ($p<0.005$).

In subjects at six selected investigational sites, baseline and termination assessments of ***total testosterone, free testosterone, sex hormone binding globulin (SHBG), and dehyroepiandrosterone sulfate (DHEAS)*** were performed. Except for the slight increase in total testosterone in the placebo group, all meaningful changes in androgens and SHBG from baseline to last available visit were observed in the ORTHO TRI-CYCLEN group. ***Analysis of covariance*** on hormone levels was performed like the lesion count analysis. Treatment differences were significant for free testosterone ($p=0.0001$), percent free testosterone ($p=0.0001$), SHBG ($p=0.0001$), and DHEAS ($p=0.0001$).

The sponsor's analysis showed that when changes from baseline to last available results were investigated, ***correlation analyses of hormones and lesion counts showed that no significant correlations*** were present in the placebo group. In the ORTHO TRI-CYCLEN group, however, some significant correlations were found. Most significant was the correlation between inflammatory lesions and free testosterone level ($p=0.0017$). This correlation could be attributable to papules since the correlation between papule count and free testosterone was approximately equally significant ($p=0.0021$). No other individual lesion count was significantly correlated with free testosterone. The papule lesion count probably contributed to the correlation between total lesions and free testosterone, also ($p=0.0439$). The only other notable relationship was the negative correlation between nodules and total testosterone and between nodules and SHBG. Regression analysis of inflammatory lesion count on free testosterone level including terms for treatment and its interaction, confirmed the fact that there was a significant correlation between free testosterone level and inflammatory lesion count ($p=0.0134$).

The same analyses of hormonal parameters that were performed for selected sites in the intent-to-treat population were also done in the evaluable-for efficacy subset. Analysis of covariance on hormone levels was performed as for the lesion count analyses. Treatment differences were significant for free testosterone ($p=0.0001$), percent free testosterone ($p=0.0001$), SHBG ($p=0.0001$), and DHEAS ($p=0.0001$). The correlation analysis for the evaluable-for efficacy population does not show the same trend pattern as was seen in the intent-to-treat population.

3. Within Cycle Variation

Based on the ORTHO TRI-CYCLEN intent-to-treat population, there were no statistically significant differences in lesion counts (inflammatory lesions, total lesions, and total comedones) among the three visits at Cycle 6. For the placebo intent-to-treat population, there were also no statistically significant differences in lesion counts (inflammatory lesions, total lesions, and total comedones) among the three visits in Cycle 6, although the means were apparently more variable.

Based on the ORTHO TRI-CYCLEN evaluable-for-efficacy population, there were no statistically significant differences in lesion counts (inflammatory lesions, total lesions, and total comedones) among the three visits at Cycle 6. For the placebo evaluable-for-efficacy population, there were also no statistically significant differences in lesion counts (inflammatory lesions, total lesions, and total comedones) among the three visits at cycle 6, although the means were apparently more variable.

f. Safety Results:

The safety results were examined for all subjects who took study medication and who had at least one on-study safety assessment. A total of 231 subjects were included in the safety analysis (118 subjects in the ORTHO TRI-CYCLEN group and 113 subjects in the placebo group). Out of 118 subjects in the ORTHO TRI-CYCLEN group, 102 subjects (86.4%) experienced a total of 446 adverse events. 94 (83.2%) of the 113 subjects in the placebo group experienced a total of 354 adverse events.

When the adverse event distribution was analyzed by system organ class, the female reproductive system accounted for the highest percentage of subjects reporting adverse events in the ORTHO TRI-CYCLEN group (50 subjects,; 42.4%), and the central and peripheral nervous system accounted for the greatest number of adverse events reported (98 occurrences; 22.0%). In the placebo group, the respiratory system accounted for the highest percentage of subjects reporting adverse events (44 subjects; 38.9%). As in the active treatment group, the greatest number of adverse events reported in the placebo group occurred in the nervous system (96 occurrences; 27.1%).

Headaches (nervous system) were the most frequently reported adverse event in both treatment groups: 31 subjects (26.3%) reported 88 events (19.7%) in the ORTHO TRI-CYCLEN group and 37 subjects (32.7%) reported 92 events (26.0%) in the placebo group.

There was no difference between treatment groups in the distribution of relationship to study drug ($p>0.05$).

The severity of the adverse events was classified by "mild," "moderate," and "marked" categories. There was no statistically significant difference between treatment groups in the distribution of severity ratings of adverse events. Twenty-four adverse events were judged to have had a substantial impact on the subjects' daily life in the ORTHO TRI-CYCLEN group (marked severity) versus 21 adverse events in the placebo group.

Eighteen subjects discontinued from the study due to an adverse event: 13 subjects (13/118; 11.0%) in the ORTHO TRI-CYCLEN group and 5 subjects (5/113; 4.4%) in the placebo group. This difference was not statistically significant.

g. Conclusions:

The results of this Phase III, randomized, double-blind, clinical trial statistically support the use of ORTHO TRI-CYCLEN as a treatment for moderate acne vulgaris. In the evaluable-for-efficacy subset, ORTHO TRI-CYCLEN was statistically significantly better than placebo for all primary measures of effectiveness; inflammatory lesion count, total lesion count, and investigator's global assessment ($p<0.05$). In the intent-to-treat analyses, ORTHO TRI-CYCLEN showed a significantly greater improvement than placebo on the inflammatory lesion count and on the investigator's global assessment. The difference between treatment groups in the total lesion count was in favor of ORTHO TRI-CYCLEN, but did not reach a level of statistical significance. The sponsor has said in their clinical report that the observed alterations in SHBG, free testosterone, and DHEAS at the conclusion of therapy in the ORTHO TRI-CYCLEN treatment group were as expected from previous observations of the drug's effect on these hormonal parameters. The sponsor further states that the safety profile seen in this study is consistent with the profile previously observed with this medication.

2. Study N93-035

This was a Phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial. The protocol, study design, efficacy and safety assessments, and statistical methods are also same as in the Study N93-034.

A. Demographic and Baseline Characteristics

A total of 257 subjects were randomized to one of two treatment groups in this study. Demographic and baseline characteristics were assessed in the 231 subjects who were evaluable for safety (i.e., subjects who took study medication and who had at least one on-study safety assessment).

The two treatment groups were not statistically different relative to age and race. The mean counts were not statistically different between the treatment groups.

B. Efficacy Results:

The efficacy analysis was performed on the intent-to-treat population, defined as the subjects who took study medication and had at least one efficacy assessment (228 subjects), and the evaluable-for-efficacy population, defined a those subjects who completed the study and who did not have major protocol variations (inadequate lesion

counts, disallowed concurrent medications, etc.) (160 subjects).

The primary efficacy parameters were: inflammatory lesions, total lesions, and investigator's global assessment. Secondary efficacy parameters included subject's end-of-therapy self-assessment and within cycle variation.

Inflammatory lesions

In the ***intent-to-treat population***, the mean inflammatory lesion count decreased from baseline to the last available results in both treatment groups. The mean change was statistically significantly greater ($p = 0.0036$) in the ORTHO TRI-CYCLEN group (9.6) than in the placebo group (5.8), a decrease from baseline of 50.2% vs. 29.0%, respectively. In the ***evaluable-for-efficacy*** population, the mean inflammatory lesion count decreased from baseline to Cycle 6 in both treatment groups. The mean change was statistically significantly greater ($p = 0.0001$) in the ORTHO TRI-CYCLEN group (11.8) than in the placebo group (7.6). The decrease from baseline was 62.0% vs. 38.6%, respectively.

Total Lesions

In the intent-to-treat population, the mean total lesion count decreased from baseline to the last available result in both treatment groups. The mean change in total lesion count was significantly greater ($p = 0.0004$) in the ORTHO TRI-CYCLEN group (23.3) than in the placebo group (11.9). The mean percentage change was 43.9% in the ORTHO TRI-CYCLEN group and 23.1% in the placebo group. Differences between treatment groups also reached statistical significance for total comedones ($p = 0.0022$), closed comedones ($p = 0.0050$), papules ($p = 0.0104$), and nodules ($p = 0.0141$). Statistical significance was not achieved for pustules ($p = .0675$).

The mean total lesion count decreased from baseline to Cycle 6 in both treatment groups in the efficacy subset. The mean change in total lesion count was significantly greater ($p = 0.0001$) in the ORTHO TRI-CYCLEN group (29.1) than in the placebo group (14.1). The mean percentage change was 53.0% in the ORTHO TRI-CYCLEN group and 26.8% in the placebo group. In addition, differences between treatment groups reached statistical significance for total comedones ($p = 0.0003$), open comedones ($p = 0.0007$), closed comedones ($p = 0.0056$), and pustules ($p = 0.0191$). Statistical significance was not reached for nodules ($p = 0.0586$).

Investigator's Global Assessment

In the intent-to-treat population, a total of 89 subjects (83.2%) in the ORTHO TRI-CYCLEN group were rated as "improved" as compared to 78 subjects (64.5%) in the placebo group. The difference between the treatment groups was statistically

significant (p=0.001). There was a significant difference (p=0.008) between treatment groups based on the five point improvement scale (excellent, good, fair, no change, worse). Thirty-one subjects (29.0%) in the ORTHO TRI-CYCLEN group as compared to 18 subjects (14.9%) in the placebo group were rated as "excellent". Thirteen subjects (12.1%) in the ORTHO TRI-CYCLEN group and 27 subjects (22.3%) in the placebo group showed no change. Five subjects (4.7%) in the ORTHO TRI-CYCLEN group and 16 subjects (13.2%) in the placebo group showed worsening of acne.

In the evaluable-for-efficacy population, 74 subjects (93.7%) in the ORTHO TRI-CYCLEN group were rated as "improved" as compared to 53 subjects (65.4%) in the placebo group. As in the intent-to-treat population, the difference between treatment groups was significant (p<0.001). There was a significant difference (p<0.001) between treatment groups based on the five point improvement scale (excellent, good, fair, no change, worse). In the ORTHO TRI-CYCLEN group, the number of subjects rated "excellent" was greater than the number of subjects in the placebo group (30/79; 38.0% in the ORTHO TRI-CYCLEN group and 15/81; 18.5% in the placebo group). Three subjects (3.8%) in the ORTHO TRI-CYCLEN group and 20 subjects (24.7%) in the placebo group showed no change in acne.

Subject's End-of therapy Self-Assessment

In the intent-to-treat population, the treatment group differences were statistically significant (p=0.025) for acne improved vs. not improved. The treatment group difference did not achieve significance (p=0.079) for the comparison of study drug to prior acne treatments (better, same, worse, no applicable). The distribution of subjects who wanted to continue the study drug at the end of the trial also did not approach statistical significance (p=0.070).

In the subjects evaluable for efficacy, the differences between treatment groups were statistically significant for all three subject end-of-therapy self-assessment parameters. First, there was a significant difference (p<0.001) in acne improved vs. not improved. The difference between treatment groups was also significant (p=0.006) regarding the comparison of study drug to prior acne treatments. Finally, the distribution of subjects who wanted to continue the study drug at the end of trial was statistically significantly greater (p=0.019) in the ORTHO TRI-CYCLEN group than the placebo group.

Within Cycle Variations

Based on the ORTHO TRI-CYCLEN intent-to-treat population, there were no statistically significant differences in lesion counts (inflammatory lesions, total lesions and total comedones) among the three visits at Cycle 6. For the placebo intent-to-treat

population, there were also no statistically significant differences in lesion counts among the three visits at Cycle 6. Within cycle variation in the evaluable-for-efficacy population was comparable to the intent-to-treat population.

C. Safety Results

The safety results were examined for all subjects who took study medication and who had at least one on-study safety assessment. A total of 231 subjects were included in the safety analysis (110 subjects in the ORTHO TRI-CYLCEN group and 121 subjects in the placebo group).

A total of 79 subjects (71.8%) in the ORTHO TRI-CYCLEN group experienced a total of 205 adverse events. Seventy-seven (64.6%) of the 121 subjects in the placebo group experienced a total of 172 adverse events.

When the adverse event distribution was analyzed by system organ class, the respiratory system accounted for the highest percentage of subjects reporting adverse events in the ORTHO TRI-CYCLEN group (30 subjects; 27.3%), and the gastro-intestinal and respiratory systems accounted for the greatest number of adverse events reported (40 occurrences; 19.5%). In the placebo group, the female reproductive system accounted for both the highest percentage of subjects reporting adverse events (24 subjects; 19.8%) and the greatest number of adverse events reported (38 occurrences; 22.1%).

The most frequently reported adverse events in the ORTHO TRI-CYCLEN group were upper respiratory tract infections (24 occurrences; 11.7%), headaches (19 occurrences; 9.3%), and nausea (17 occurrences; 8.3%). The most frequently reported adverse events in the placebo group were headaches (16 occurrences; 9.3%) and upper respiratory tract infections (13 occurrences; 7.6%). Nausea occurred only 4 times (2.3%) in the placebo group.

There was no apparent difference between treatment groups in the distribution of adverse event relationship to study drug. There was no apparent difference between treatment groups in the distribution of severity ratings of adverse events. Seven adverse events (7/205); 3.4%) were judged to have had a marked impact on the subject's daily life in the ORTHO TRI-CYCLEN group versus 6 adverse events (6/172; 3.5%) in the placebo group.

D. Conclusions:

In the intent-to treat and evaluable-for-efficacy analyses, ORTHO TRI-CYCLEN showed a significantly greater improvement for all primary efficacy measures: total lesion count, inflammatory lesion count, and investigator's global assessment. The sponsor is of the opinion that the safety profile seen in this study is consistent with the profile previously observed with this medication.

III Conclusions (which may be conveyed to the sponsor)

The results of ***Study N93-034*** statistically support the use of ORTHO TRI-CYCLEN as a treatment for moderate acne vulgaris. In the ***evaluable-for-efficacy subset, ORTHO TRI-CYCLEN was statistically significantly better than placebo for all primary measures of effectiveness; inflammatory lesion count, total lesion count, and investigator's global assessment ($p<0.05$).*** In the ***intent-to-treat analyses, ORTHO TRI-CYCLEN showed a significantly greater improvement than placebo on the inflammatory lesion count and on the investigator's global assessment. The difference between treatment groups in the total lesion count was in favor of ORTHO TRI-CYCLEN, but did not reach a level of statistical significance.*** The sponsor has said in their clinical report that the observed alterations in SHBG, free testosterone, and DHEAS at the conclusion of therapy in the ORTHO TRI-CYCLEN treatment group were as expected from previous observations of the drug's effect on these hormonal parameters. ***The safety profile seen in this study is consistent with the profile previously observed with this medication.***

The results of ***Study N93-035*** statistically support the use of ORTHO TRI-CYCLEN as a treatment for moderate acne vulgaris. In the intent-to treat and evaluable-for-efficacy analyses, ORTHO TRI-CYCLEN showed a significantly greater improvement for all primary efficacy measures: total lesion count, inflammatory lesion count, and investigator's global assessment. The safety profile seen in this study is consistent with the profile previously observed with this medication.

Thus, these two studies statistically support the use of ORTHO TRI-CYCLEN as a treatment for moderate acne vulgaris. The safety profile seen in this study is consistent with the profile previously observed with this medication.

8/28/96

R. Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

Ralph Harkins 8/12/96

Concur: Ralph Harkins, Ph.D
Division Director, Biometrics IV

cc:

Archival NDA 20681
HFD-540
HFD-540/Mr. White
HFD-540/Dr. Wilkin
HFD-540/Dr. Katz
HFD-540/Dr. Toombs
HFD-540/Dr. Harkins
HFD-540/Dr. Srinivasan
HFD-540/Dr. Pierce
Chron.

This review contains 16 pages.

Srinivasan/WP Text/Windows 3.1/7-2077/August 22, '96/c:\reviews.nda\Orthotri.nda

OCT 8 1996

Norgestimate/Ethinyl Estradiol
Ortho Tri-Cyclen® Tablets
NDA 20-681
Reviewer: E.D. Bashaw, Pharm.D.
APW

R.W. Johnson Pharm. Res.
Raritan, NJ

Submission Date:
12-26-95

Review of a Type 6 NDA

Background

Ortho Tri-Cyclen® Tablets are currently approved under NDA 19-697 as an oral contraceptive agent. It is sold as a dose-pak containing either 21 or 28 tablets. It obtained its name Tri-Cyclen® as a play on words relating to its changing ratio of ingredients across the 21 or 28 day regimen. This change in the amount and ratio of progestin:estrogen component is designed to approximate the natural fluctuations in female hormones associated with ovulation and menses. The oral contraceptive indication was approved back in 1991. This current NDA has been submitted to the Division of Dermatological and Dental Drug Products as a treatment for moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy. As this represents only the addition of a new indication to an approved drug product, this NDA has been submitted as a Type 6 application.

Human Pharmacokinetics and Biopharmaceutics

At the present time the sponsor has submitted no in vivo or in vitro pharmacokinetic information in support of this application. As both the dose and the target population (i.e. females) has not changed, there are no relevant biopharmaceutic issues unique to this indication. In addition, the sponsor is not making any alterations in the pharmacokinetic portion of the approved package insert. On the basis of this there are no pharmacokinetic issues to be addressed with this application.

A review of the file on this NDA has revealed that there are still two outstanding issues from the original approval of this product under NDA 19-697. In Dr. Chuck Bradley's review of March 8, 1991 a number of deficiencies were noted in the application. Since that time all but two of them have been addressed satisfactorily. The remaining issues will be summarized below:

1. **Dissolution**-In the original review of the NDA the sponsor was proposing the use of a method. Since then the sponsor has been engaged by the Division of Biopharmaceutics and its successor the Division of Pharmaceutical Evaluation-II in a dialog to develop a non-alcoholic method. In a review dated 5/28/96, Dr. Angelica Dorantes of DPE-II indicated that an acceptable method had been found but that additional validation data was needed. This issue is rapidly coming to conclusion and no further input is warranted.

2. **Dose proportionalitiy**-In the original review the sponsor was cited with a deficiency for only performing single dose bioavailability trials. Given that

plasma levels of both components are essentially undetectable following a single dose, the sponsor was asked to conduct a steady-state, dose proportionality trial as a phase IV commitment. According to the file an acceptable protocol was received and subsequently reviewed. The Agency is still awaiting the final results of this trial. While not a requirement of approval for this application the Agency should follow-up with the sponsor as to the timing of the submission of these results.

Besides these two outstanding issues, both of which progress is being made on completion, there are no other outstanding biopharmaceutic issues pending for either this NDA (20-681) or the original NDA (19-697).

Labeling

No labeling revisions are required in the pharmacokinetic section as they relate to this indication. Once the results of the aforementioned dose proportionality study are available, the label should be revised to reflect the current policy of the Office of Clinical Pharmacology and Biopharmaceutics. As primary responsibility of this label rests with DPE-II, no action will be taken at this time.

Recommendation

The application contains no in vivo or in vitro biopharmaceutic information for review and based on the lack of changes in dosing and target population none is required. On this basis the application is acceptable to the Division of Pharmaceutical Evaluation-III.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-540)
Division of Pharmaceutical Evaluation-III

Secondary Review, JA Larson ~~Niek Fleischer, Ph.D.~~ 6/8/96

CC: NDA 20-681 (ORIG),
HFD-540/DIV File
HFD-540/CSO/White
HFD-880(Bashaw)
HFD-880(Fleischer)
HFD-870 (Clarence Bott, Drug, Chron Files)
HFD-344(Viswanathan)

AUG 2 1996

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

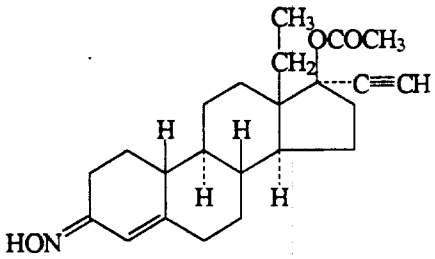
NDA No.: 20-681

Date Submitted: 12-26-95
Date CDER Received: 12-26-95
Date Assigned: 1-4-96
Date Review Completed: 4-4-96
Date Review Accepted by Supervisor:

Name of Drug: Ortho Tri-Cyclen (norgestimate/ethinyl estradiol)

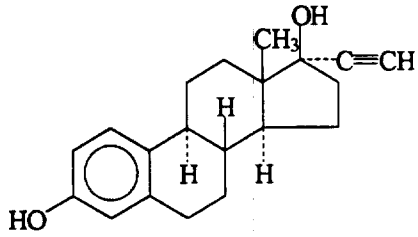
Structure:	formula	molecular weight
norgestimate	$C_{23}H_{31}NO_3$	369.5

(18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetoxy)-13-ethyl-,oxime, (17α)-(+)-)



ethinyl estradiol $C_{20}H_{24}O_2$ 296.4

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



Pharmacological Category: combined oral contraceptive

Sponsor: The R.W. Johnson Pharmaceutical Research Institute
920 Rt. 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Indication: moderate acne vulgaris

Route of Administration: oral

Formulation: Ortho Tri-Cyclen 21 (white, light blue, and blue) and Ortho Tri-Cyclen 28 (white, light blue, blue, and green) tablets

white tablet 0.180 mg norgestimate, 0.035 mg ethinyl estradiol
(inactive ingredients include lactose, magnesium stearate, and pregelatinized starch)

light blue tablet 0.215 mg norgestimate, 0.035 mg ethinyl estradiol
(inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch)

blue tablet 0.250 mg norgestimate, 0.035 mg ethinyl estradiol
(inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch)

green tablet no active ingredients
(inactive ingredients include D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch)

Related INDs/NDAs: INDs ; NDAs 19,697, 19,653

SUMMARY

No new nonclinical data regarding pharmacology or toxicology were submitted. The label is consistent with that for the already approved product. The dosage and target population are unchanged from the original indication. There is no recommendation as to the duration of therapy for the acne indication alone in the absence of any need or desire for oral contraception.

The adverse effects of Ortho Tri-Cyclen and other oral contraceptives have been described in laboratory animals and humans. In the studies submitted with NDAs 19,653 and 19,697, a number of dose-dependent lesions were seen. In the 10 year monkey study, animals (16 per dose group) were treated for 4 years with 2.5 µg/kg norgestimate/0.5 µg/kg ethinyl estradiol, or at 10

or 50 times that dose. Control animals were untreated. For the last 6 years of the study, animals received [redacted] µg/kg norgestimate/[redacted] µg/kg ethinyl estradiol, or at 10 or 50 times that dose. The low dose for the last 6 years was the same as the human dose on a mg/kg basis and 3 times the human dose on a mg/m^2 basis. Adverse effects that were dose-related in incidence or appeared only in the high dose groups were as follows:

- ♦ increased platelet count;
- ♦ an irreversible, significant increase in SGPT (SALT) (The reviewer of the study stated in his review that this is known to occur in women taking oral contraceptives);
- ♦ increased weights of liver, pituitary, and kidney;
- ♦ decreased ovarian weight;
- ♦ gross pathological lesions in liver, heart, and kidney, and masses in the cervix, vaginal wall, and mammary gland;
- ♦ histopathological lesions, including vaginal epithelial atrophy and mucosal metaplasia, lobular hyperplasia of mammary glands, pituitary hypertrophy and/or hyperplasia, myocardial multifocal fibrosis, chronic interstitial nephritis, hepatic necrosis, pancreatic islet cell hyperplasia, and brain gliosis;
- ♦ one each of the following neoplasias in the highest dose group, considered to be related to treatment: adenocarcinoma of the cervix, leiomyoma of the vaginal wall, carcinoma *in situ* of the mammary gland, and a mammary adenoma;
- ♦ one each of the following neoplasias in the middle dose group, considered to be related to treatment: urinary bladder papilloma, pituitary angiofibroma, and pituitary capillary angioma.

In the 7-year dog study, uterine tumors were diagnosed in two high-dose animals. The original histopathological diagnoses on these were leiomyosarcoma and carcinosarcoma. Because of the serious nature of many of the above lesions, nonapproval was originally recommended. The sponsor then submitted some of the tissues to an outside panel of experts for re-evaluation. Liver lesions in the monkeys were reclassified as microgranulomas unassociated with drug treatment. Liver necrosis in three high-dose monkeys was determined to be due to causes other than drug administration. The cervical tumor in a high-dose monkey was reclassified as an endocervical tumor not of endometrial origin, and was considered to be spontaneous and not drug-related. The uterine tumors in dogs were reclassified as leiomyomas, both with no evidence of malignancy. Some of the issues of concern at that time were not addressed, such as the mammary gland lesions in the monkey. Non-malignant neoplasias were still acknowledged.

The information contained in the package insert for Ortho Tri-Cyclen includes warnings regarding thromboembolic and cardiovascular disorders, elevation of blood pressure, carcinoma of reproductive organs and breast, hepatic neoplasia, gallbladder effects, ocular lesions, effects on carbohydrate and lipid metabolism, and use during early pregnancy. In the sponsor's studies and in published reports, norgestimate has been shown to have less androgenic activity than other progestins used in combined oral contraceptives and to lack adverse effects on carbohydrate and lipid metabolism.

A few studies in animals investigating the effects of combined oral contraceptives have appeared in the recent literature. One model of contraceptive-induced hepatocellular carcinoma in female Wistar rats has been developed that indicates that ethinyl estradiol and norethindrone acetate act as both initiators and promoters (Ogawa et al., 1995). Another study demonstrated

DNA adduct formation, hyperplasia and hepatocellular carcinoma in female Wistar rats receiving ethinyl estradiol orally (Shimomura et al., 1992). A dose-response relationship has been established for ethinyl estradiol as a promotor of hepatocellular adenoma and carcinoma in rats (Campen et al., 1990). Ethinyl estradiol was shown to induce cell proliferation or to promote tumors in livers of Sprague-Dawley rats (Yager et al., 1984; Mayol et al., 1992). Alcohol ingestion was shown to enhance hepatocarcinogenesis in Wistar rats administered ethinylestradiol and norethindrone acetate (Yamagiwa et al., 1994). Ethinyl estradiol has been shown to induce hepatocellular carcinomas (Li and Li, 1984; *ibid.*, 1987) and renal tumors (Li et al., 1995) in Syrian hamsters. Induction of increased levels of the liver and bone isozymes of ALP by norethisterone:ethinyl estradiol (100:7) was demonstrated in rats and was attributed to ethinyl estradiol (Ohno et al., 1994). In rhesus monkeys, a long term study on the effects of a number of synthetic oral contraceptive steroids on mammary gland morphology revealed a high rate of occurrence of proliferative atypias and carcinomas, suggesting a carcinogenic effect (Tavassoli et al., 1988). Also in rhesus monkeys, there is a report of embryotoxicity in animals receiving norethindrone acetate and ethinyl estradiol (Prahalada and Hendrickx, 1983). No teratogenicity was observed, but the prenatal mortality rate was significantly higher than in control animals. An *in vitro* study in rat hepatocyte cultures demonstrated that treatment with steroids containing a 17α-ethinyl substituent caused an increase in unscheduled DNA synthesis (Blakey and White, 1985). Genotoxicity testing of ethinyl estradiol:norethisterone acetate revealed positive results in the chromosomal aberration assay and negative results in the mouse micronucleus test (Shyama et al., 1991).

In human females, oral contraceptives may act as tumor promoters in the development of breast cancer (Buehring, 1988). In epidemiological studies examining the use of low estrogen dose/new generation progestin combined oral contraceptives, there is an apparent increased risk of breast cancer in young women who began to use oral contraceptives at an early age (<18-25 years) and used them long-term (>4-10 years), and in women using oral contraceptives before their first full term pregnancy (Tyrer, 1993; Kjaer et al., 1993; White et al., 1994; Brinton et al., 1995; Bagshaw, 1995), an increased risk of cervical cancer, and an increased risk of primary liver cancer, especially with long-term use (Vessey et al., 1983; Brock et al., 1989; Brinton et al., 1990; Bagshaw, 1995). Leiomyomas have been observed in patients taking oral contraceptives long-term (up to 17 years); this has been reproduced in animal models (Dallenbach, et al., 1989). However, in the case of the newer products, combining a third generation progestin (of which norgestimate is one) with a low dose estrogen, it is too early to estimate the long-term cancer risks.

An increase in the incidence of hepatocellular adenomas and carcinomas in women has been associated with long-term use of oral contraceptives (Nissen et al., 1979; Steinbrecher et al., 1981; Buhler et al., 1982; Christensen et al., 1986; Grigsby et al., 1987; Ferrarra and Rutland, 1988, Kenya, 1990; Korula et al., 1991; Hsing et al., 1992). These tumors may spontaneously rupture and hemorrhage into the peritoneal cavity; they have also been found to regress when use of the contraceptive drugs is discontinued. Reports of mesenchymal neoplasms in the liver, such as rhabdomyosarcoma, have also been reported to be associated with long-term oral contraceptive use (Cote and Urmacher, 1990).

Recently, attention has been directed at the third generation progestins and their association with venous thromboembolism (VTE). The use of first and second generation

progestins are associated with an increased risk of these events relative to that in non-users, even when the drug is combined with a low dose estrogen component (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1995a,b). The use of third generation progestins is associated with increased risk of VTE relative to that with use of a second generation progestin, with a case fatality rate of 1-2% (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1995a), resulting in approximately 1 death in 1 million users each year (Weiss, 1995). The incidence rates for idiopathic cardiovascular death in another study were estimated to be 4.3 per 100,000 users of levonorgestrel (a second generation progestin and a metabolite of norgestimate; 22±6% of the norgestimate dose is systemically available as levonorgestrel; Kuhnz et al., 1994), and up to 4.8 for other third generation progestins in combined oral contraceptive users. Cases of nonfatal VTE were 16.1 per 100,000 for levonorgestrel and up to 29.3 for the third generation progestins examined (Jick et al., 1995).

Acne has been reported as a side effect of this product (Runnebaum et al., 1992).

COMMENTS

Systemic availability of ethinyl estradiol has been reported to be 40% of the orally administered dose in humans, but only to be 3, 0.3, 9, and 0.6% of an intragastrically administered dose in rats, rabbits, dogs, and rhesus monkeys, respectively (Dusterberg et al., 1986), administered as a [redacted]mg/ml microcrystalline suspension in Myrj-saline to rats, rabbits, and monkeys and as a mixture of 1 mg micronized ethinyl estradiol:[redacted] mg of lactose in gelatine capsules in dogs. The authors cite radiolabelled studies that indicate 100% of the dose to be absorbed, and indicate that the remainder must be lost to biotransformation in the gut wall and hepatic first-pass metabolism. Consequently, a 100-fold difference in dose between an animal study and human use may not represent that great a difference in systemic exposure.

In light of the incidence of and/or suspected relationship of combined oral contraceptives to an increased incidence hepatic adenoma/carcinoma, mammary gland carcinomas, cervical and uterine tumors, and blood clotting abnormalities in women taking these drugs, the appearance of the same type of lesions or clinical signs suggestive of such lesions, even in the absence of malignancy, in the animal studies may be reason for concern.

The current label justifies the risk of serious adverse effects by comparing the risk of death as a consequence of side effects of oral contraceptive agents to the risk of death related to childbirth. For most age groups, that comparison favors the use of these drugs. However, the risk of adverse effects, particularly those that may be serious or life-threatening, may not be justified by the benefit of acne control alone.

While it is not uncommon for oral contraceptives to be used in the treatment of acne, none of those listed in the 1995 PDR included that indication in their label. If approved, Ortho Tri-Cyclen may be the first oral contraceptive approved for the acne indication.

A number of questions remain. What effect would these drugs have on the normal growth and maturation of adolescents if begun at an earlier age than would be expected for contraception? If this also results in longer total lifetime use of the drug, what additional risks does its use pose? Since Ortho Tri-Cyclen has only been marketed for a short period of time, there is no long-term epidemiological data from users of this particular product.

Other drugs used in the treatment of acne include retinoids and antibiotics, such as tetracycline and erythromycin. Drug interaction studies have primarily addressed loss of contraceptive efficacy. There is a concern that antibiotics may interfere with enterohepatic recirculation of the ethinyl estradiol or induce enzymes responsible for the metabolic clearance of oral contraceptive drugs. This may result in side effects and/or reduced contraceptive efficacy. When retinoids are administered, the use of contraception is advised due to the risk of teratogenicity of the retinoid; if antibiotics or other concurrent medication may decrease contraceptive efficacy, then alternative methods would need to be considered. In this case the use of the oral contraceptive would be for acne alone. Additionally, acetaminophen may result in an increase in the plasma concentration of ethinyl estradiol (Fazio, 1991); if acetaminophen is taken frequently, this may lead to an exacerbation of estrogen-related side effects.

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REGULATORY CONCLUSION

Based on the incidence and severity of adverse effects in nonclinical animal studies at or near clinically relevant exposures, Ortho Tri-Cyclen approval for the proposed indication alone would not be recommended. The medical officer will make the final assessment of the risk vs. benefit of Ortho Tri-Cyclen for the proposed indication.

RECOMMENDATIONS

Should the product be approved, some label modifications may need to be made:

1. Under "Indications", the label states, "Oral contraceptives are highly effective," immediately after stating that the drug is indicated for the treatment of acne. Since contraceptive efficacy is discussed in the remainder of the paragraph, "*in the prevention of pregnancy*" should be added to that sentence, and another statement related to efficacy in the treatment of acne alone may be more appropriately placed later in the section when that indication is discussed.

2. Additions should be made to the label regarding drug interactions (see reviews by D'Arcy, 1986 and Fazio, 1991), since acne patients may also be taking antibiotics or retinoids, elaborating on the potential for loss of contraceptive efficacy and potential toxicity in the case of drugs with which clearance is reduced by oral contraceptives, both in the physician's package insert and in the instructions to patients.

3. A maximum duration of treatment for the acne indication alone, in the absence of a need or wish for contraception should be stated.

The sponsor should be informed that, if not previously performed and submitted, genotoxicity testing of the components and the combination product should be done as a Phase IV study.

Amy C. Nostrandt 4/12/96
Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

cc:
NDA 20,681
HFD-340
HFD-540
HFD-540/PHARM/ANostrandt
HFD-540/SPHARM/AJacobs
HFD-540/MO/EToombs
HFD-540/CHEM/JHiggins
HFD-540/PMS/KDWhite

Concurrence Only:
HFD-540/DD/WILKIN

HFD-540/SPHARM/JACOBS concurred 4/15/96

As above, except for "regulatory conclusion" and the third paragraph under "comments" which imply that acne control benefits may be outweighed by the side effect profile of this product. Some acne is extremely severe and greatly damages the quality of the patient's existence. As pointed out by the reviewer, the medical officer will need to evaluate the risk-benefit ratio for acne and its subsets 4/15/96.

NOV 27 1996

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-681 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11/13/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/26/95	12/26/96	8/28/96
AMENDMENT/BC	1/24/96	1/25/96	8/28/96
AMENDMENT/BC	11/11/96	11/13/96	11/13/96

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

DRUG PRODUCT NAME

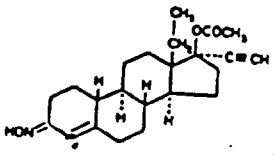
Proprietary:	ORTHO TRI-CYCLEN
Nonproprietary/USAN:	Norgestimate + Ethinyl Estradiol
Code Names/#'s:	RJW 10131
Chem.Type/Ther.Class:	6 S

ANDA Suitability Petition/DESI/Patent Status:
N/A

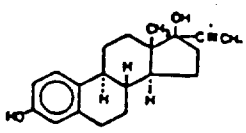
PHARMACOL.CATEGORY/INDICATION: Treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, OL.WT:

Norgestimate:
18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17-alpha)-(±)-.



Ethinyl estradiol:
19-Nor-17alpha-pregna-1,3,5(10)-trien-20-yne-3,17-diol.



EMPIRICAL FORMULA:
Norgestimate: $C_{23}H_{31}NO_3$

Ethinyl estradiol: $C_{20}H_{24}O_2$

MOLECULAR WEIGHT:
Norgestimate: 369.5
Ethinyl estradiol: 296.41

SUPPORTING DOCUMENTS:
N/A

RELATED DOCUMENTS (if applicable):
IND
IND
NDA 19-697 RWJ (Ortho Tri-Cyclen); Approved 7/3/92
NDA 19-653 RWJ (Ortho Tri-Cyclen 28); Approved 12/29/89

CONSULTS:

Sent EA review and FONSI to HFD-357 on 11/4/96 for concurrence.

REMARKS/COMMENTS:

The applicant filed an NDA in accordance with 21 CFR 314.50, 21 CFR 314.54 and agreements made during a pre-NDA meeting of 9/25/95. This NDA is the subject of a marketed product, Ortho Tri-Cyclen (NDA 19-697) and is being submitted as a new indication to the presently approved product. The NDA only contains Clinical and Statistical Data in support of the application. Since no changes have been made in the manufacturing of the currently approved product, no Chemistry, Manufacturing and Controls information was submitted. However, the applicant has cross-referenced NDA 19-697 for information relating to chemistry, manufacturing, and controls used in that NDA. Note: The CMCs were found approvable for NDA 19-697 [see Chemist Review #2 (HFD-510) dated 3/30/90].

Environmental Assessment: A type 6 NDA for Ortho Tri-Cyclen requires an Environmental Assessment in accordance with regulation 21 CFR Part 25.22 (a)(14). In this regard, the applicant provided EA information as per this regulation. This EA information was reviewed and found acceptable to draft a FONSI report on 11/1/96 (see EA reviews dated 10/1/96 and 11/1/96). EA reviews and FONSI was sent to Nancy Sager (HFD-357) on 11/13/96 for concurrence. In this regard, the FONSI was signed by Nancy Sager on 11/17/96.

Establishment Evaluation Review:

EERs (ID #9388) were requested on 2/26/96 for the following facilities: (1) R W Johnson, 920 Route 202 South, Raritan, NJ;

These facilities were found acceptable for GMPs

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approved for manufacturing and controls under section 505 of the Act.

EERs: All manufacturing facilities are currently in acceptable GMP compliance

Environmental Assessment: Acceptable. EA reviews dated 10/1/96 and 11/13/96 and FONSI dated 11/13/96 were sent to Nancy Sager (HFD-357) on 11/13/96 for concurrence. In this regard, the FONSI was signed by Nancy Sager on 11/17/96.

Labeling: Review of labeling was not required from technical standpoint because the drug product is a commercially available product.

Ernest G. Pappas 11/26/96

Ernest G. Pappas,
Review Chemist

cc: Orig. NDA 20-681
HFD-540/Division File
HFD-540/Pappas
HFD-540/Toombs
HFD-540/Nostradt
HFD-540/White
HFD-540/DeCamp

11/26/96

11/27/96

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

[ORTHO TRI-CYCLEN]
[norgestimate/ethinyl estradiol]

[Tablets]

NDA 20-681

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-540

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-681

ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an internal part of its regulatory process.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets, The R.W. Johnson Pharmaceutical Research Institute has prepared an environmental assessment in accordance with 21 CFR 25.31a ~~(b)(3)~~ (attached)] which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Insignificant quantities of either the drug substance or drug product are expected to enter the environment. Disposal will normally take place in landfills or by incineration.

Norgestimate/ethinyl estradiol tablets is a marketed product. The drug product is manufactured by Ortho Pharmaceutical Corporation. The ingredients used to manufacture this product are not cited as hazardous and/or toxic air pollutants. The applicant's facilities operate in conformance with current Good Manufacturing Practices, and employ appropriate procedural and technological measures to control air, liquid, and solid emission waste streams. The drug's intended use is for "Treatment of moderate acne vulgaris in females who have no known contraindication to oral contraceptive therapy".

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility or landfill. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/13/96 Ernest G. Pappas
DATE PREPARED BY
Ernest G. Pappas
Chemist
HFD-540/HFD-830

11/13/96 David Morton Reynolds, Ph.D. for DeCamp
DATE DIVISION CONCURRENCE
Wilson H. DeCamp, Ph.D
Supervisory Chemist
HFD-540/HFD-830

11/17/96 Nancy B Sager
DATE CONCURRED
Nancy B. Sager
Environmental Scientist
Office of the Center Director
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)
NON-CONFIDENTIAL EA

CC: Original NDA 20-681/HFD-540
HFD-540/Pappas
HFD-540/Decamp
HFD-540/White
HFD-104/FONSI File [NDA 20-681]
HFD-104/Docket File
HFD-019/FOI Copy

NON-CONFIDENTIAL ENVIRONMENTAL ASSESSMENT

Changes to the original EA dated October 15, 1986:

I.	**DATE:**	January 24, 1996
II.	**NAME OF APPLICANT:**	The R.W. Johnson Pharmaceutical Research Institute
III.	**ADDRESS:**	No changes from the original EA
IV.	**PROPOSED ACTION**	

Type 6 New Drug Application (NDA) for ORTHO TRI-CYCLEN® Tablets. Environmental Assessment required by 21 CFR Part 25.22 (a)(14).

ORTHO TRI-CYCLEN Tablets, a widely prescribed oral contraceptive, is also indicated in the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy.

The drug substances, norgestimate and ethinyl estradiol, are available through outside vendors. The drug product will be manufactured and packaged by Ortho-McNeil Pharmaceutical in Raritan, NJ and by

The product will be dispensed, through physician prescription, in clinic, hospital, and home health care settings, and by pharmacies.

Disposal of prescribed product will be primarily through use, with returned product and production wastes containing the active ingredients disposed through high temperature incineration at licensed disposal facilities. Wastewater from the manufacturing process will be disposed through permitted discharge to the local Publicly Owned Treatment Works in New Jersey and Puerto Rico.

V. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

No changes from original Environmental Assessment.

VI. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

This product, ORTHO TRI-CYCLEN Tablets, has been in full-scale production for approximately three years with no apparent environmental effects. It is not expected that this action will result in environmental releases of the drug substances or excipients above their current levels.

The production process is the same at both manufacturing facilities, and consists of the following steps: granulation, milling, blending, compression, and packaging. Each of these steps has been evaluated for the potential to release the active as an air contaminant, with all deemed capable of generating insignificantly small amounts of airborne emissions. Washing operations result in small amounts of waterborne emissions.

Air Releases

The existing manufacturing area is equipped with a general exhaust ventilation system with a rated removal efficiency rate of 99.9%. In addition, the processing equipment has been designed to operate such that airborne emissions are either not generated, or if they are generated, that these emissions are controlled using state-of-the-art pollution control equipment. The manufacturing process is expected to limit production losses to less than 2 kg/batch. Of this, less than 0.5 kg is into the air, and the controls described above will limit actual environmental releases to air of the actives to less than 0.002 g/batch. Filters will be cleaned with hot water, with the resultant washings discharged to the plant's wastewater stream. Filter

media contaminated with the active ingredient will be disposed through high temperature incineration (1600-1800 °F) at a commercial solid waste incinerator.

With the approval of this action, ORTHO TRI-CYCLEN Tablets production in Raritan and Manati is expected to be batches/year (5th year production schedule), which includes batches of each of the three strengths that make up the regimen. This yields estimated airborne releases of the active ingredients of approximately g/year. In actuality, releases would effectively be zero.

Water Releases

Waterborne releases into the facility's treatment plant are likely to occur from the cleaning of process equipment and air filters containing the entrapped active. After product removal at the end of the batch run, the process vessels are cleaned following a standard cleaning procedure. A hot water rinse is applied to remove any residual product from the processing equipment. Although the cleaning frequency changes with production scheduling, it is expected to occur once every 2 batches. For purposes of this assessment it will be assumed that the production equipment will be cleaned after every batch. This cleaning operation is expected to release approximately 1.5 kg/batch of product, containing approximately 4.5 grams of active ingredients, into the facility's wastewater stream, which will ultimately be diluted to near zero by the time it reaches the environment. As stated above, with the approval of this action, ORTHO TRI-CYCLEN Tablets production in Raritan and Manati is expected to be

batches/year, which yields estimated waterborne releases of approximately g/year.

Disposal of Waste from Use

To meet patient demands, the 5th year production estimate for the drug product will require kg of drug substance. Assuming disposal will occur through wastewater collection systems, an estimate of the Maximum Expected Emitted Concentration (MEEC) yields an environmental concentration of $\times 10^{-}$ mg/L. This production will also result in an expected introduction concentratioin (EIC) entering the aquatic environment of $\times 10^{-}$ mg/L. Material discarded by the consumer will be incinerated or landfilled at sanitary/municipal solid waste facilities.

Returned goods will be received and managed by Ortho-McNeil Pharmaceutical Corporation's Distribution Center in Bridgewater, New Jersey. Disposal of product will be through high temperature incineration at a commercially licensed incinerator. It is Ortho-McNeil's policy to destroy all returned products in this fashion. The high temperature of incineration (>1600 °F) is expected to destroy the active ingredient, with the resultant ash posing no environmental hazard. This practice insures that returned goods are managed in an environmentally sound manner.

VII. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

No changes from original Environmental Assessment.

VIII. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Second sentance to read: Manufacture of the product will not produce significant air emissions of drug substance, and maximum water emissions...

IX. USE OF RESOURCES AND ENERGY

No changes from original Environmental Assessment.

X. MITIGATION MEASURES

No changes from original Environmental Assessment.

XI. ALTERNATIVES TO THE PROPOSED ACTION

No changes from original Environmental Assessment.

XII. LIST OF PREPARERS

The following should be added to the list of preparers:

Christopher A. DeSantos
Senior Environmental Engineer
Ortho-McNeil Pharmaceutical
1000 Route 202
Raritan, New Jersey 08869-0602

Five and a half years of professional environmental experience; four within the pharmaceutical industry, and one and a half in environmental consulting.

XIII. CERTIFICATION

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for the preparation of the Environmental Assessment.

Date: January 24, 1996

Signature: Christyn A. DeSa

Title: Senior Environmental Engineer

XIV. REFERENCES

No changes from original Environmental Assessment.

Environmental Assessment for Norgestimate 180 µg Plus Ethinyl Estradiol 35 µg Tablets

1. Date: October 15, 1986

2. Name of Applicant: Ortho Pharmaceutical Corporation

3. Address of Applicant: U. S. Route 202, P. O. Box 300
Raritan, NJ 08869-0602

4. Proposed Action: New Drug Approval for Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets. Environmental Assessment required by 21CFR 314.50 (d) (1) (iii)

The new drug substance, Norgestimate, will be used in combination with the currently used contraceptive steroid, Ethinyl Estradiol, in a ratio of 180 µg Norgestimate to 35 µg Ethinyl Estradiol in the product Norgestimate 180 plus EE 35. Norgestimate will be obtained from outside suppliers, with the new product manufactured at the Ortho Pharmaceutical Corporation facility in Raritan, New Jersey and the Ortho Pharmaceuticals, Incorporated facility in Manati, Puerto Rico. The product will be used, through physician prescription, in hospital, clinic, and home environments. Disposal of prescribed product will be through use, with returned product and manufacturing waste disposed through high temperature incineration at the Ortho Pharmaceutical Corporation plant site in Raritan, NJ, or through contract disposal facilities. Wash water from manufacturing will be disposed through permitted discharge to the primary and secondary wastewater treatment facilities at the local Publicly Owned Treatment Works in New Jersey and in Puerto Rico.

5. Nomenclature for New Drug Substance

a. Norgestimate

USAN: norgestimate

Chemical Names:

[1] (+)-17-(acetyloxy)-13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime

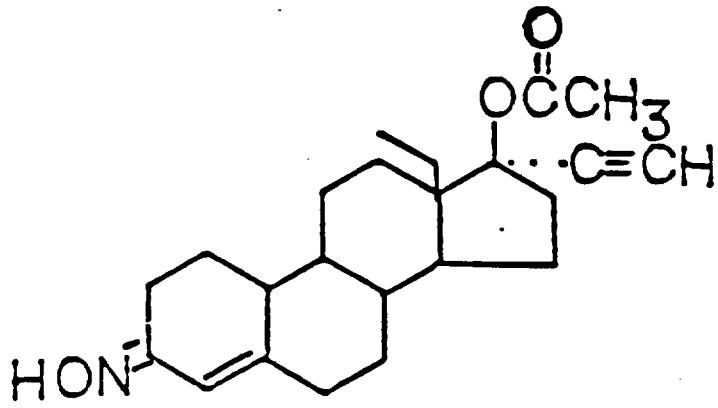
[2] (+)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one-oxime acetate (ester)

Ortho Pharmaceutical Corporation Code: ORF 10131 AND 10131-00

CAS Registry Number: 35189-28-7

Molecular Weight: 369.51

Structural Formula



Empirical Formula: $C_{23}H_{31}NO_3$

Physical Description: White to almost white powder, free or virtually free of visible foreign matter.

Impurities: Total impurities not greater than 1%.

Additives: None

Product containing the new drug substance: Consisting of Norgestimate and Ethinyl Estradiol USP in combination with the following commonly used excipients:*

Lactose NF (Anhydrous)

Pregelatinized Starch, NF

Magnesium Stearate, NF

*Quantitative composition located in Chemistry, Manufacturing and Controls Technical section of this NDA. Such information is trade secret and confidential.

b. Ethinyl Estradiol

USAN : Ethinyl Estradiol, USP*

CAS Registry Number : 57-63-6

Code Designation : ORF 1403

Chemical Names:

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

[2] 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

*As agreed by Dr. D. Kertesz and Mr. M. Bennet during the pre-NDA meeting dated September 17, 1986, no additional physical chemical and stability data for ethinyl estradiol, USP will be submitted in this NDA. For information on ethinyl estradiol please refer to our MODICON® 21 NDA #17-488 and all supplements thereto, which was approved October 15, 1974.

6. Introduction of Substances Into the Environment from Manufacturing

The substances listed in Section 5 of the Environmental Assessment represent the materials that may be emitted into the environment from manufacturing Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets. The potential emissions are from washwater released into the water via wastewater treatment. Particulates are not emitted into the environment from the manufacturing process due to a closed, filtered air handling system.

Particulates may be generated through addition of ingredients to the process vessel. Dry ingredients are added to the process vessel in a procedure that may evolve particulates. The particulates are passed through a dust collector, with 99% removal efficiency, and two banks of High Efficiency Particulate Air (HEPA) filters. The filtered air is returned to the building environment with no emission to the outside.

Emission of the new drug substance to the water will result from cleaning of the process vessels. Following product removal, the process vessels are cleaned and rinsed with purified water. Small amounts of product are contained in the washwater, which combines with the remainder of the effluent from the site and is sent to the municipal wastewater treatment plant for primary and secondary treatment.

The discharges of these materials in New Jersey are regulated by the Federal Water Pollution Control Regulations, the New Jersey water Pollution Control Laws, and the Boro of Raritan Sewer Use Ordinance. The discharges of these materials in Puerto Rico are regulated by the Federal Water Pollution Control Regulations, the Puerto Rico Water Pollution

Control Laws, and the Barcelonetta Sewer Use Regulations. Approval of the New Drug Application is not expected to produce any impacts on Ortho Pharmaceutical's continued compliance with these laws, regulations, and ordinances.

The product is very similar in composition and function to products currently produced at both Ortho facilities. These products have no negative impact on the ability of the Corporation to comply with emission standards. Approval of the application for Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets will not add to the emission rate at the facilities in a manner that will result in non-compliance.

Raritan Facility

Air emissions will not occur from production of this product. This is due to a closed air handling in which exhaust air from production is filtered and returned to the process systems rather than discharged to the environment. The air filtration system consists of a dust collector system with 99% removal efficiency, followed by two HEPA filters connected in series, each with 99.97% removal efficiency. The system filters particulates generated by addition of powdered ingredients in manufacturing the product. The filtered air is then returned to the process building. Collected particulates and filter media are disposed through high temperature incineration.

Water emissions are calculated to be parts per million (PPM) product in the effluent leaving the facility. This is based upon an expected loss of kg of product in the washwater (% of batch weight), being mixed into the 70,000 gallon per day facility discharge. The amount that

would reach the treatment plant would be parts per billion (PPB), based upon the treatment plant capacity of 20 million gallons per day.

Norgestimate is present in the product in concentrations of 0.18% and Ethinyl Estradiol is present in concentrations of 0.035%. The amount of the active in the wastewater at the facility discharge is PPB Norgestimate and PPB Ethinyl Estradiol. The amount at the sewerage plant would be PPB Norgestimate and PPB for Ethinyl Estradiol. Since neither Norgestimate nor Ethinyl Estradiol is regulated as an environmental pollutant, these levels in the emissions would not affect compliance at the Raritan facility.

Manati Facility

Air emissions will not occur from production of this product due to an air handling system very similar to that discussed above being in place at the Manati facility.

Water emissions are calculated to be PPM product in the effluent leaving the facility. This is based upon an expected loss of kg of product in the washwater, being mixed into the 15,000 gallon per day facility discharge. The amount that would reach the treatment plant would be PPB, based upon the treatment plant capacity of 8.3 million gallons per day.[2]

The amount of Norgestimate in the wastewater at the facility discharge would be PPB and the amount of the sewerage treatment plant would be PPB. The amount of Ethinyl Estradiol in the wastewater at the facility discharge would be PPB and the amount at the sewerage

treatment plant would be PPB. Since Norgestimate and Ethinyl estradiol are not regulated as environmental pollutants, these levels in the emissions would not affect compliance at the Manati Facility.

Consumer Use

Release of the material to the environment is not expected from use of the product. Since the material is completely consumed in the use, no emission of Norgestimate nor Ethinyl Estradiol should occur from use of the new product.

Disposal of Waste from Manufacturing and Use

The material requiring disposal would include returned goods and manufacturing waste. All waste materials will be disposed by high temperature incineration at Ortho Pharmaceutical Corporation's Raritan, New Jersey facility or through contract vendors. Assuming a 10% ash content from destruction of the waste, 40 kg of ash will be generated for every batch or its equivalent incinerated. Based upon current practices with existing product, less than kg of ash per year will require disposal. The ash will consist of carbon and inorganic salts. The high temperatures of the incinerator (in excess of 1000 °F) would destroy the active ingredient, with the resultant ash presenting no expected environmental concerns.

Air emissions from incineration of the product are not expected to contain active ingredient. Tests on the emissions from the Ortho incinerator on other products containing contraceptive steriods showed no steroid present at parts per trillion detection levels.[3]

7. Fate of Emitted substances in the Environment

As discussed in Section 6 of the Environmental Assessment, the environmental concentrations of the product are expected to be very low. The levels of Norgestimate and Ethinyl Estradiol in the environment through manufacture, use, and disposal of the product are expected to be virtually non-detectable in environmental samples.

Raritan Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be PPB. The amount of Ethinyl Estradiol is calculated to be PPB. This is based upon the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 400.[1] No adverse impact is expected from this concentration.

Manati Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be PPB. The amount of Ethinyl Estradiol is calculated to be PPB. This is based on the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 375.[2] No adverse impact is expected from this concentration.

Emission form Use and Disposal

Emission of the product to the land is not expected due to disposal by high temperature incineration. The incineration of the product will destroy the material, with approximately 2 cubic yards of ash yearly resulting from the incineration. The ash will be inert and present no

threat to the environment. Disposal of unused product by the consumer is expected to present minimal impact to the environment. The amount of material in the product package corresponds with the prescribed regimen of use, and thus the product should be consumed through use rather than be disposed in unused form. In addition, the expense of the product will encourage use rather than disposal.

Degradation in the Environment

The emission levels discussed above represent the maximum expected environmental concentrations of Norgestimate (PPB or µg/liter of water). These levels assume no treatment or biodegradation in the environment. However, significant reductions of these levels should occur through biological degradation in the wastewater treatment plant and in the environment.

There is extensive literature on the biodegradation of steroidal compounds by naturally occurring microoganisms. These studies[4,5,6] show a wide variety of microbes that effectively metabolize and degrade steroids through side chain removal and ring cleavage. Soil and other environmentally occurring micro-organisms are responsible for this biodegradation and provide an effective means to biodegrade any emitted active compound from manufacturing the new product.

The environment is additionally provided protection due to the metabolism of the active ingredients by higher organisms. Pharmacologic studies[7] on the actives show no unexpected metabolic products. As such, biological metabolism of Norgestimate and Ethinyl Estradiol should readily occur with the production of no adverse impacts to the environment.

8. Environmental Effects of Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets

The calculations for the emission of the new drug substance, Norgestimate, and the other active ingredient Ethinyl Estradiol, indicate that the maximum expected environmental concentrations will be very low. Manufacture of the product will not produce air emissions, and maximum water emissions are expected to be µg/l of Norgestimate and µg/l of Ethinyl Estradiol from either facility. Due to further dilution and biodegradation in the environment, the concentrations of Norgestimate and Ethinyl Estradiol in the ambient environment will be many orders of magnitude lower. A comparison of the toxicological data for Norgestimate plus Ethinyl Estradiol with the expected maximum environmental concentration of the actives indicates that no adverse environmental impacts are expected from the manufacture, use, and disposal of Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets.

Toxicological studies[7] for Norgestimate and Norgestimate plus Ethinyl Estradiol assessed the following:

a. Acute Toxicity;
b. Sub-chronic toxicity;
c. Chronic toxicity;
d. Reproductive effects and teratology;
e. Mutagenicity; and,
f. Carcinogenicity.

Acute Toxicity

The studies assessed the toxicity of Norgestimate and Norgestimate in

combination with Ethinyl Estradiol (5:1) administered via the oral and intravenous routes. The species studied were mice, Long Evans rats, and beagle dogs. The (LD_{50}) for oral administration of Norgestimate and Norgestimate plus Ethinyl Estradiol (5:1) was greater than 5000 mg/kg. Since the maximum expected environmental concentration of the actives at the point of environmental release is µg/l for Norgestimate and µg/l for Ethinyl Estradiol, the acute toxic dose is billion times greater than the maximum expected environmental concentration of these compounds in one liter of water. It is virtually impossible for an acute toxic reaction to occur from environmental release of Norgestimate plus Ethinyl Estradiol.

Sub-Chronic Toxicity

Studies were done assessing the toxicity of sub-chronic doses of Norgestimate and Norgestimate plus Ethinyl Estradiol in female Long Evans rats, female beagle dogs and female Rhesus monkeys. The doses were orally administered for three months as follows:

Rats - 0.5, 1.0, 2.5, or 10.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Rats - 0.55, 1.10, 2.75, or 11.0 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Dogs - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Dogs - 0.28, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Monkeys - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 9.5% carboxymethylcellulose suspension; and,

Monkeys - 0.275, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10:1)/kg/day in 0.5% carboxymethylcellulose suspensions.

The administration of Norgestimate and Norgestimate plus Ethinyl Estradiol in the dosage levels listed above resulted in physiological changes consistent with the activity of contraceptive steroids. Lower dosage levels resulted in less profound changes, and the studies noted no unexpected effects for the compound.

The lowest dosage level in the study, 0.25 mg/kg/day resulted in no unexpected adverse physiological impacts. This level is extremely large when compared with the maximum expected environmental concentrations of Norgestimate and Ethinyl Estradiol. The 0.25 mg is more than times greater than the maximum environmental levels of the actives. The levels in the environment are not expected to present any sub-chronic toxic effects.

Chronic Toxicity

Studies were conducted using female Long Evans rats, beagle dogs, and Rhesus monkeys for a period of one to two years. The doses were administered on a regimen that mimicked human use patterns using dosages of Norgestimate plus Ethinyl Estradiol in a 5:1 ratio.

The dosages in the rat studies ranged from 0.019 mg/kg/day to 3.0 mg/kg/day and represent 6.25 to 1000 times the strength of the human dose. Dosages in the dog and monkey studies ranged from 0.06 to 0.6 mg/kg/day, representing 20 to 200 times the strength of the human dose.

The administration of the compounds to the test subjects resulted in physiological changes expected from the pharmacologic effects of contraceptive steroids. The low and moderate dosage levels resulted in no significant changes while a significant response did occur only in the very high dosage level. The very high dosage (1000 times human dose) resulted in an increase of mammary gland adenocarcinomas of the rats. No increase in mammary gland adenocarcinomas was noted in all other dosage levels.

The lowest dosage level, 0.019 mg/kg/day, which resulted in no unexpected adverse reactions, represents a level times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol in one liter of water. The highest dosage level in all tests, which represents the only dosage level which resulted in a significant adverse effect, increasing mammary gland adenocarcinoma, is more than million times larger than the maximum expected environmental concentrations of Norgestimate plus Ethinyl Estradiol in one liter of water. Based upon these observations, it is highly unlikely that the environmental releases of the actives from manufacturing or use will present chronic toxicity concerns.

Reproductive Effects and Teratology

Tests in female Long Evans rats indicated that administration of Norgestimate plus Ethinyl Estradiol (5:1) resulted in physiological changes consistent with administration of contraceptive steroids. The results indicate a dose response relationship directly correlated to the strength of the dose, with higher doses resulting in more profound effects.

Additionally, the tests indicated that the formulation did not produce teratogenic effects in the tested subjects. The tests did produce evidence of embryotoxicity in high dosage levels, but these embryotoxic effects did not occur in low dose levels.

The low dose levels in the studies, 0.03 mg/kg/day, produced physiological results consistent with those expected from administration of this class of compounds. No adverse effects were noted at the low dosage level, which is approximately times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol. Environmental releases are not expected to result in adverse reproductive impacts.

Mutagenicity

Mutagenic potential for Norgestimate plus Ethinyl Estradiol (7:1) was assessed using in vitro (Ames), and in vivo (Sister Chromatid Exchange, Mouse Micronucleus) test methods. The tests showed no mutagenic potential for doses as high as 114 mg/kg in vivo. In Vitro tests at very high levels of actives also showed no mutagenic potential. The levels assessed for mutagenic potential represent levels approximately million times greater than the maximum expected environmental concentrations of the substances. Environmental releases of Norgestimate plus Ethinyl Estradiol should present no mutagenic potential.

Carcinogenicity

As discussed in the section on chronic toxicity, mammary gland adenocarcinomas did occur in rats treated with very high doses of

Norgestimate plus Ethinyl Estradiol. These levels represent 1000 times the expected therapeutic dose and million times the expected maximum environmental concentration of Norgestimate. Lower dose levels, also significantly higher than the expected therapeutic dose and expected maximum environmental concentration, showed no evidence of an increased risk of developing mammary gland adenocarcinomas. Long term studies in dogs (7 years) and monkeys (10 years) showed the occurrence of 1 leiomyosarcoma of the uterus in the dog at high dose level (25 times the therapeutic dose and times the expected maximum environmental concentrations) and 1 mucoepidermoid carcinoma of the cervix in the monkey at high dose level (50 times the therapeutic dose and times the expected maximum environmental concentrations). These changes are known to occur spontaneously and the test data suggest that these tumors may be spontaneous occurrences. It is highly improbable that environmental releases of Norgestimate will result in an increased incidence of these carcinomas. Environmental release of Norgestimate from manufacture, use, or disposal does not appear to present a carcinogenicity concern.

Effects on Plant Life

The toxicology data does not assess potential effect on plant life. The compounds are specific in their activity and are not expected to adversely affect plant life. In addition, the very low concentrations in the environment and the biodegradability of the materials would mitigate any potential for adverse effects on plant life.

Environmental Effects Summary

There appears to be very little potential for adverse environmental effects from releases of Norgestimate plus Ethinyl Estradiol. The combination of very low environmental concentrations, probable biodegradability, relatively low toxicity, and lack of mutagenic potential indicate that no adverse impacts should result from the manufacture, use, or disposal of Norgestimate plus Ethinyl Estradiol.

9. Use of Resources and Energy:

The production of Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets will use processes and equipment presently used for similar products. The production of the product will require a commitment of those materials, listed in Section 5 for each batch of product manufactured. A commitment of fossil fuel will be required for production, transportation, and disposal of the product. No new land use commitments will be required for the manufacture of the product and a yearly land use commitment of less than 2 cubic yards of landfill space will be needed for the disposal of incinerator ash from incineration of the returned goods and off specification material. No adverse impacts are expected on endangered species nor registered historic places.

10. Mitigation Measures:

No adverse impacts are anticipated from production, use, and disposal of Norgestimate 180 µg plus Ethinyl Estradiol 35 µg Tablets. All necessary pollution control measures are in place for production, use, and disposal of the product.

11. Alternatives to Proposed Action:

No alternatives to the proposed action have been identified as necessary.

14. References

1. Somerset Raritan Valley Sewerage Authority Industrial Pretreatment Program Technical Report; Metcalf and Eddy, Inc./Engineers, 1984.
2. Personal communication with Mr. Carl Axel Soderberg, Puerto Rico Environmental Quality Board.
3. Emissions evaluation of the Kelly Waste Incinerator Exhaust, Ortho Pharmaceutical Corporation; Betz, Converse, and Murdock Engineers Inc., 1982.
4. Mahato, S. and Mukherjee, A. Steroid Transformations by Microorganisms, Phytochemistry, Vol 23, No. 10, pp 2132-2154, 1984.
5. Kieslich, K. and Sebek, O.K. Microbial Transformation of Organic Compounds; Alkanes, Alicyclics, Terpenes, and Alkaloids. Annual Report on Fermentation Processes, 1:267-297, 1979.
6. Charney, W. and Herzog, H.L. Microbial Transformations of Steriods; a Handbook. Academic Press, New York 1969.
7. Complete information on Pharmacology and Toxicology contained elsewhere in the New Drug Application.

Environmental Assessment for Norgestimate 215 µg Plus Ethinyl Estradiol 35 µg Tablets

1. Date: October 15, 1986

2. Name of Applicant: Ortho Pharmaceutical Corporation

3. Address of Applicant: U. S. Route 202, P. O. Box 300
Raritan, NJ 08869-0602

4. Proposed Action: New Drug Approval for Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets. Environmental Assessment required by 21CFR 314.50 (d) (1) (iii)

The new drug substance, Norgestimate, will be used in combination with the currently used contraceptive steroid, Ethinyl Estradiol, in a ratio of 215 µg Norgestimate to 35 µg Ethinyl Estradiol in the product Norgestimate 215 plus EE 35. Norgestimate will be obtained from outside suppliers, with the new product manufactured at the Ortho Pharmaceutical Corporation facility in Raritan, New Jersey and the Ortho Pharmaceuticals, Incorporated facility in Manati, Puerto Rico. The product will be used, through physician prescription, in hospital, clinic, and home environments. Disposal of prescribed product will be through use, with returned product and manufacturing waste disposed through high temperature incineration at the Ortho Pharmaceutical Corporation plant site in Raritan, NJ, or through contract disposal facilities. Wash water from manufacturing will be disposed through permitted discharge to the primary and secondary wastewater treatment facilities at the local Publicly Owned Treatment Works in New Jersey and in Puerto Rico.

5. Nomenclature for New Drug Substance

a. Norgestimate

USAN: norgestimate

Chemical Names:

[1] (+)-17-(acetyloxy)-13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime

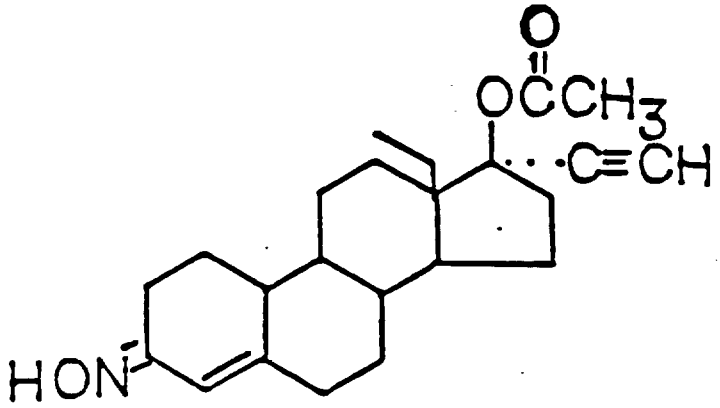
[2] (+)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one-oxime acetate (ester)

Ortho Pharmaceutical Corporation Code: ORF 10131 AND 10131-00

CAS Registry Number: 35189-28-7

Molecular Weight: 369.51

Structural Formula



Empirical Formula: $C_{23}H_{31}NO_3$

Physical Description: White to almost white powder, free or virtually free of visible foreign matter.

Impurities: Total impurities not greater than 1%

Additives: None

Product containing the new drug substance: Consisting of Norgestimate and Ethinyl Estradiol USP in combination with the following commonly used excipients:*

Lactose NF (Anhydrous)

Pregelatinized Starch, NF

Magnesium Stearate, NF

FD&C Blue #2 Aluminum Lake (13%)

*Quantitative composition located in Chemistry, Manufacturing and Controls Technical section of this NDA. Such information is trade secret and confidential.

b. Ethinyl Estradiol

USAN: Ethinyl Estradiol, USP*

CAS Registry Number: 57-63-6

Code Designation: ORF 1403

Chemical Names:

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

[2] 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

*As agreed by Dr. D. Kertesz and Mr. M. Bennet during the pre-NDA meeting dated September 17, 1986, no additional physical chemical and stability data for ethinyl estradiol, USP will be submitted in this NDA. For information on ethinyl estradiol please refer to our MODICON® 21 NDA #17-488 and all supplements thereto, which was approved October 15, 1974.

6. Introduction of Substances Into the Environment from Manufacturing

The substances listed in Section 5 of the Environmental Assessment represent the materials that may be emitted into the environment from manufacturing Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets. The potential emissions are from washwater released into the water via wastewater treatment. Particulates are not emitted into the environment from the manufacturing process due to a closed, filtered air handling system.

Particulates may be generated through addition of ingredients to the process vessel. Dry ingredients are added to the process vessel in a procedure that may evolve particulates. The particulates are passed through a dust collector, with 99% removal efficiency, and two banks of High Efficiency Particulate Air (HEPA) filters. The filtered air is returned to the building environment with no emission to the outside.

Emission of the new drug substance to the water will result from cleaning of the process vessels. Following product removal, the process vessels are cleaned and rinsed with purified water. Small amounts of product are contained in the washwater, which combines with the remainder of the effluent from the site and is sent to the municipal wastewater treatment plant for primary and secondary treatment.

The discharges of these materials in New Jersey are regulated by the Federal Water Pollution Control Regulations, the New Jersey water Pollution Control Laws, and the Boro of Raritan Sewer Use Ordinance. The discharges of these materials in Puerto Rico are regulated by the Federal Water Pollution Control Regulations, the Puerto Rico Water Pollution

Control Laws, and the Barcelonetta Sewer Use Regulations. Approval of the New Drug Application is not expected to produce any impacts on Ortho Pharmaceutical's continued compliance with these laws, regulations, and ordinances.

The product is very similar in composition and function to products currently produced at both Ortho facilities. These products have no negative impact on the ability of the Corporation to comply with emission standards. Approval of the application for Norgestimate 215 mg plus Ethinyl Estradiol 35 mg Tablets will not add to the emission rate at the facilities in a manner that will result in non-compliance.

Raritan Facility

Air emissions will not occur from production of this product. This is due to a closed air handling in which exhaust air from production is filtered and returned to the process systems rather than discharged to the environment. The air filtration system consists of a dust collector system with 99% removal efficiency, followed by two HEPA filters connected in series, each with 99.97% removal efficiency. The system filters particulates generated by addition of powdered ingredients in manufacturing the product. The filtered air is then returned to the process building. Collected particulates and filter media are disposed through high temperature incineration.

Water emissions are calculated to be parts per million (PPM) product in the effluent leaving the facility. This is based upon an expected loss of kg of product in the washwater (% of batch weight), being

mixed into the 70,000 gallon per day facility discharge. The amount that would reach the treatment plant would be parts per billion (PPB), based upon the treatment plant capacity of 20 million gallons per day.

Norgestimate is present in the product in concentrations of .0.215% and Ethinyl Estradiol is present in concentrations of 0.035%. The amount of the active in the wastewater at the facility discharge is PPB Norgestimate and PPB Ethinyl Estradiol. The amount at the sewerage plant would be PPB Norgestimate and PPB for Ethinyl Estradiol. Since neither Norgestimate nor Ethinyl Estradiol is regulated as an environmental pollutant, these levels in the emissions would not affect compliance at the Raritan facility.

Manati Facility

Air emissions will not occur from production of this product due to an air handling system very similar to that discussed above being in place at the Manati facility.

Water emissions are calculated to be PPM product in the effluent leaving the facility. This is based upon an expected loss of kg of product in the washwater, being mixed into the 15,000 gallon per day facility discharge. The amount that would reach the treatment plant would be PPB, based upon the treatment plant capacity of 8.3 million gallons per day.[2]

The amount of Norgestimate in the wastewater at the facility discharge would be PPB and the amount of the sewerage treatment plant would be PPB. The amount of Ethinyl Estradiol in the wastewater at the

facility discharge would be PPB and the amount at the sewerage treatment plant would be PPB. Since Norgestimate and Ethinyl estradiol are not regulated as environmental pollutants, these levels in the emissions would not affect compliance at the Manati Facility.

Consumer Use

Release of the material to the environment is not expected from use of the product. Since the material is completely consumed in the use, no emission of Norgestimate nor Ethinyl Estradiol should occur from use of the new product.

Disposal of Waste from Manufacturing and Use

The material requiring disposal would include returned goods and manufacturing waste. All waste materials will be disposed by high temperature incineration at Ortho Pharmaceutical Corporation's Raritan, New Jersey facility or through contract vendors. Assuming a 10% ash content from destruction of the waste, 40 kg of ash will be generated for every batch or its equivalent incinerated. Based upon current practices with existing product, less than kg of ash per year will require disposal. The ash will consist of carbon and inorganic salts. The high temperatures of the incinerator (in excess of 1000 °F) would destroy the active ingredient, with the resultant ash presenting no expected environmental concerns.

Air emissions from incineration of the product are not expected to contain active ingredient. Tests on the emissions from the Ortho incinerator on other products containing contraceptive steriods showed no steroid present at parts per trillion detection levels.[3]

7. Fate of Emitted substances in the Environment

As discussed in Section 6 of the Environmental Assessment, the environmental concentrations of the product are expected to be very low. The levels of Norgestimate and Ethinyl Estradiol in the environment through manufacture, use, and disposal of the product are expected to be virtually non-detectable in environmental samples.

Raritan Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be PPB. The amount of Ethinyl Estradiol is calculated to be PPB. This is based upon the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 400.[1] No adverse impact is expected from this concentration.

Manati Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be PPB. The amount of Ethinyl Estradiol is calculated to be PPB. This is based on the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 375.[2] No adverse impact is expected from this concentration.

Emission form Use and Disposal

Emission of the product to the land is not expected due to disposal by high temperature incineration. The incineration of the product will destroy the material, with approximately 2 cubic yards of ash yearly resulting from the incineration. The ash will be inert and present no

threat to the environment. Disposal of unused product by the consumer is expected to present minimal impact to the environment. The amount of material in the product package corresponds with the prescribed regimen of use, and thus the product should be consumed through use rather than be disposed in unused form. In addition, the expense of the product will encourage use rather than disposal.

Degradation in the Environment

The emission levels discussed above represent the maximum expected environmental concentrations of Norgestimate (PPB or µg/liter of water). These levels assume no treatment or biodegradation in the environment. However, significant reductions of these levels should occur through biological degradation in the wastewater treatment plant and in the environment.

There is extensive literature on the biodegradation of steroidal compounds by naturally occurring microoganisms. These studies[4,5,6] show a wide variety of microbes that effectively metabolize and degrade steroids through side chain removal and ring cleavage. Soil and other environmentally occurring micro-organisms are responsible for this biodegradation and provide an effective means to biodegrade any emitted active compound from manufacturing the new product.

The environment is additionally provided protection due to the metabolism of the active ingredients by higher organisms. Pharmacologic studies [7] on the actives show no unexpected metabolic products. As such, biological metabolism of Norgestimate and Ethinyl Estradiol should readily occur with the production of no adverse impacts to the environment.

8. Environmental Effects of Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets

The calculations for the emission of the new drug substance, Norgestimate, and the other active ingredient Ethinyl Estradiol, indicate that the maximum expected environmental concentrations will be very low. Manufacture of the product will not produce air emissions, and maximum water emissions are expected to be µg/l of Norgestimate and µg/l of Ethinyl Estradiol from either facility. Due to further dilution and biodegradation in the environment, the concentrations of Norgestimate and Ethinyl Estradiol in the ambient environment will be many orders of magnitude lower. A comparison of the toxicological data for Norgestimate plus Ethinyl Estradiol with the expected maximum environmental concentration of the actives indicates that no adverse environmental impacts are expected from the manufacture, use, and disposal of Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets.

Toxicological studies[7] for Norgestimate and Norgestimate plus Ethinyl Estradiol assessed the following:

a. Acute Toxicity;
b. Sub-chronic toxicity;
c. Chronic toxicity;
d. Reproductive effects and teratology;
e. Mutagenicity; and,
f. Carcinogenicity.

Acute Toxicity

The studies assessed the toxicity of Norgestimate and Norgestimate in combination with Ethinyl Estradiol (5:1) administered via the oral and intravenous routes. The species studied were mice, Long Evans rats, and beagle dogs. The (LD_{50}) for oral administration of Norgestimate and Norgestimate plus Ethinyl Estradiol (5:1) was greater than 5000 mg/kg. Since the maximum expected environmental concentration of the actives at the point of environmental release is μg/l for Norgestimate and μg/l for Ethinyl Estradiol, the acute toxic dose is billion times greater than the maximum expected environmental concentration of these compounds in one liter of water. It is virtually impossible for an acute toxic reaction to occur from environmental release of Norgestimate plus Ethinyl Estradiol.

Sub-Chronic Toxicity

Studies were done assessing the toxicity of sub-chronic doses of Norgestimate and Norgestimate plus Ethinyl Estradiol in female Long Evans rats, female beagle dogs and female Rhesus monkeys. The doses were orally administered for three months as follows:

Rats - 0.5, 1.0, 2.5, or 10.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Rats - 0.55, 1.10, 2.75, or 11.0 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Dogs - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Dogs - 0.28, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Monkeys - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 9.5% carboxymethylcellulose suspension; and,

Monkeys - 0.275, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10:1)/kg/day in 0.5% carboxymethylcellulose suspensions.

The administration of Norgestimate and Norgestimate plus Ethinyl Estradiol in the dosage levels listed above resulted in physiological changes consistent with the activity of contraceptive steroids. Lower dosage levels resulted in less profound changes, and the studies noted no unexpected effects for the compound.

The lowest dosage level in the study, 0.25 mg/kg/day resulted in no unexpected adverse physiological impacts. This level is extremely large when compared with the maximum expected environmental concentrations of Norgestimate and Ethinyl Estradiol. The 0.25 mg is more than times greater than the maximum environmental levels of the actives. The levels in the environment are not expected to present any sub-chronic toxic effects.

Chronic Toxicity

Studies were conducted using female Long Evans rats, beagle dogs, and Rhesus monkeys for a period of one to two years. The doses were administered on a regimen that mimicked human use patterns using dosages of Norgestimate plus Ethinyl Estradiol in a 5:1 ratio.

The dosages in the rat studies ranged from 0.019 mg/kg/day to 3.0 mg/kg/day and represent 6.25 to 1000 times the strength of the human

dose. Dosages in the dog and monkey studies ranged from 0.06 to 0.6 mg/kg/day, representing 20 to 200 times the strength of the human dose.

The administration of the compounds to the test subjects resulted in physiological changes expected from the pharmacologic effects of contraceptive steroids. The low and moderate dosage levels resulted in no significant changes while a significant response did occur only in the very high dosage level. The very high dosage (1000 times human dose) resulted in an increase of mammary gland adenocarcinomas of the rats. No increase in mammary gland adenocarcinomas was noted in all other dosage levels

The lowest dosage level, 0.019 mg/kg/day, which resulted in no unexpected adverse reactions, represents a level times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol in one liter of water. The highest dosage level in all tests, which represents the only dosage level which resulted in a significant adverse effect, increasing mammary gland adenocarcinoma, is more than million times larger than the maximum expected environmental concentrations of Norgestimate plus Ethinyl Estradiol in one liter of water. Based upon these observations, it is highly unlikely that the environmental releases of the actives from manufacturing or use will present chronic toxicity concerns.

Reproductive Effects and Teratology

Tests in female Long Evans rats indicated that administration of Norgestimate plus Ethinyl Estradiol (5:1) resulted in physiological changes consistent with administration of contraceptive steroids. The

results indicate a dose response relationship directly correlated to the strength of the dose, with higher doses resulting in more profound effects.

Additionally, the tests indicated that the formulation did not produce teratogenic effects in the tested subjects. The tests did produce evidence of embryotoxicity in high dosage levels, but these embryotoxic effects did not occur in low dose levels.

The low dose levels in the studies, 0.03 mg/kg/day, produced physiological results consistent with those expected from administration of this class of compounds. No adverse effects were noted at the low dosage level, which is approximately times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol. Environmental releases are not expected to result in adverse reproductive impacts.

Mutagenicity

Mutagenic potential for Norgestimate plus Ethinyl Estradiol (7:1) was assessed using in vitro (Ames), and in vivo (Sister Chromatid Exchange, Mouse Micronucleus) tests methods. The tests showed no mutagenic potential for doses as high as 114 mg/kg in vivo. In Vitro tests at very high levels of actives also showed no mutagenic potential. The levels assessed for mutagenic potential represent levels approximately 285 million times greater than the maximum expected environmental concentrations of the substances. Environmental releases of Norgestimate plus Ethinyl Estradiol should present no mutagenic potential.

Carcinogenicity

As discussed in the section on chronic toxicity, mammary gland adenocarcinomas did occur in rats treated with very high doses of Norgestimate plus Ethinyl Estradiol. These levels represent 1000 times the expected therapeutic dose and million times the expected maximum environmental concentration of Norgestimate. Lower dose levels, also significantly higher than the expected therapeutic dose and expected maximum environmental concentration, showed no evidence of an increased risk of developing mammary gland adenocarcinomas. Long term studies in dogs (7 years) and monkeys (10 years) showed the occurrence of 1 leiomyosarcoma of the uterus in the dog at high dose level (25 times the therapeutic dose and times the expected maximum environmental concentrations) and 1 mucoepidermoid carcinoma of the cervix in the monkey at high dose level (50 times the therapeutic dose and times the expected maximum enviromental concentrations). These changes are known to occur spontaneously and the test data suggest that these tumors may be spontaneous occurrences. It is highly improbable that environmental releases of Norgestimate will result in an increased incidence of these carcinomas. Environmental release of Norgestimate from manufacture, use, or disposal does not appear to present a carcinogenicity concern.

Effects on Plant Life

The toxicology data does not assess potential effect on plant life. The compounds are specific in their activity and are not expected to adversely affect plant life. In addition, the very low concentrations in the environment and the biodegradability of the materials would mitigate any potential for adverse effects on plant life.

Environmental Effects Summary

There appears to be very little potential for adverse environmental effects from releases of Norgestimate plus Ethinyl Estradiol. The combination of very low environmental concentrations, probable biodegradability, relatively low toxicity, and lack of mutagenic potential indicate that no adverse impacts should result from the manufacture, use, or disposal of Norgestimate plus Ethinyl Estradiol.

9. Use of Resources and Energy:

The production of Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets will use processes and equipment presently used for similar products. The production of the product will require a commitment of those materials, listed in Section 5 for each batch of product manufactured. A commitment of fossil fuel will be required for production, transportation, and disposal of the product. No new land use commitments will be required for the manufacture of the product and a yearly land use commitment of less than 2 cubic yards of landfill space will be needed for the disposal of incinerator ash from incineration of the returned goods and off specification material. No adverse impacts are expected on endangered species nor registered historic places.

10. Mitigation Measures:

No adverse impacts are anticipated from production, use, and disposal of Norgestimate 215 µg plus Ethinyl Estradiol 35 µg Tablets. All necessary pollution control measures are in place for production, use, and disposal of the product.

11. Alternatives to Proposed Action:

No alternatives to the proposed action have been identified as necessary.

12. Preparer:

Timothy McGuinness

Environmental Engineer

Ortho Pharmaceutical Corporation

Eight years of professional experience, five with the New Jersey Department of Environmental Protection and three with Ortho Pharmaceutical Corporation.

Bachelor degree in Microbiology plus graduate study in Chemical Engineering, Biochemistry and Microbiology.

Certified Hazardous Material Manager

13. Certification:

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for preparation of the Environmental Assessment.

Date _____

Signature _____

Title _____

14. References

1. Somerset Raritan Valley Sewerage Authority Industrial Pretreatment Program Technical Report; Metcalf and Eddy, Inc./Engineers, 1984.
2. Personal communication with Mr. Carl Axel Soderberg, Puerto Rico Environmental Quality Board.
3. Emissions evaluation of the Kelly Waste Incinerator Exhaust, Ortho Pharmaceutical Corporation; Betz, Converse, and Murdock Engineers Inc., 1982.
4. Mahato, S. and Mukherjee, A. Steroid Transformations by Microorganisms, Phytochemistry, Vol 23, No. 10, pp 2132-2154, 1984.
5. Kieslich, K. and Sebek, O.K. Microbial Transformation of Organic Compounds; Alkanes, Alicyclics, Terpenes, and Alkaloids. Annual Report on Fermentation Processes, 1:267-297, 1979.
6. Charney, W. and Herzog, H.L. Microbial Transformations of Steriods; a Handbook. Academic Press, New York 1969.
7. Complete information on Pharmacology and Toxicology contained elsewhere in the New Drug Application.

Environmental Assessment for Norgestimate 250 mcg Plus Ethinyl Estradiol 35 mcg Tablets

1. Date: October 15, 1986

2. Name of Applicant: Ortho Pharmaceutical Corporation

3. Address of Applicant: U. S. Route 202, P. O. Box 300
Raritan, NJ 08869-0602

4. Proposed Action: New Drug Approval for Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets. Environmental Assessment required by 21CFR 314.50 (d) (1) (iii)

The new drug substance, Norgestimate, will be used in combination with the currently used contraceptive steroid, Ethinyl Estradiol, in a ratio of 250 mcg. Norgestimate to 35 mcg. Ethinyl Estradiol in the product Norgestimate 250 plus EE 35. Norgestimate will be obtained from outside suppliers, with the new product manufactured at the Ortho Pharmaceutical Corporation facility in Raritan, New Jersey and the Ortho Pharmaceuticals, Incorporated facility in Manati, Puerto Rico. The product will be used, through physician prescription, in hospital, clinic, and home environments. Disposal of prescribed product will be through use, with returned product and manufacturing waste disposed through high temperature incineration at the Ortho Pharmaceutical Corporation plant site in Raritan, NJ, or through contract disposal facilities. Wash water from manufacturing will be disposed through permitted discharge to the primary and secondary wastewater treatment facilities at the local Publicly Owned Treatment Works in New Jersey and in Puerto Rico.

5. Nomenclature for New Drug Substance

USAN: norgestimate

Chemical Names:

[1] (+)-17-(acetyloxy)-13-ethyl-18,19-dinor-
17 α-pregn-4-en-20-yn-3-one oxime

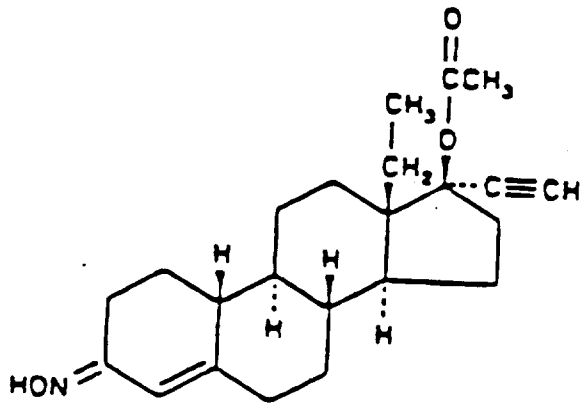
[2] (+)-13-ethyl-17-hydroxy-18,19-dinor-
17 α-pregn-4-en-20-yn-3-one oxime acetate (ester)

Ortho Pharmaceutical Corporation Code: ORF 10131 AND 10131-00

CAS Registry Number: 35189-28-7

Molecular Weight: 369.51

Structural Formula



Empirical Formula: $C_{23}H_{31}NO_3$

Physical Description: White to almost white powder, free or virtually free of visible foreign matter.

Impurities: The sum of all impurities is <1% maximum with no individual impurity greater than 0.5%

Additives: None

Product containing the new drug substance: Consisting of Norgestimate and Ethinyl Estradiol USP in combination with the following commonly used excipients:*

Lactose, NF (Anhydrous)

Pregelatinized Starch, NF

Magnesium Stearate, NF

FD&C Blue #2 Aluminum Lake (13%)

*Quantitative composition located in Chemistry, Manufacturing and Controls Technical section of this NDA. Such information is trade secret and confidential.

USAN : Ethinyl Estradiol, USP*

CAS Registry Number : 57-63-6

Code Designation : ORF 1403

Chemical Names:

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

[2] 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

*As agreed by Dr. D. Cortez and Mr. M. Bennet during the pre-NDA meeting dated September 17, 1986, no additional physical chemical and stability data for ethinyl estradiol, USP will be submitted in this NDA. For information on ethinyl estradiol please refer to our MODICON® 21 NDA #17-488 and all supplements thereto, which was approved October 15, 1974.

6. Introduction of Substances Into the Environment from Manufacturing

The substances listed in section 5 of the Environmental Assessment represent the materials that may be emitted into the environment from manufacturing Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets. The potential emissions are from washwater released into the water via wastewater treatment. Particulates are not emitted into the environment from the manufacturing process due to a closed, filtered air handling system.

Particulates may be generated through addition of ingredients to the process vessel. Dry ingredients are added to the process vessel in a procedure that may evolve particulates. The particulates are passed through a dust collector, with 99% removal efficiency, and two banks of High Efficiency Particulate Air (HEPA) filters. The filtered air is returned to the building environment with no emission to the outside.

Emission of the new drug substance to the water will result from cleaning of the process vessels. Following product removal, the process vessels are cleaned and rinsed with purified water. Small amounts of product are contained in the washwater, which combines with the remainder of the effluent from the site and is sent to the municipal wastewater treatment plant for primary and secondary treatment.

The discharges of these materials in New Jersey are regulated by the Federal Water Pollution Control Regulations, the New Jersey water Pollution Control Laws, and the Boro of Raritan Sewer Use Ordinance. The

discharges of these materials in Puerto Rico are regulated by the Federal Water Pollution Control Regulations, the Puerto Rico Water Pollution Control Laws, and the Barcelonetta Sewer Use Regulations. Approval of the New Drug Application is not expected to produce any impacts on Ortho Pharmaceutical's continued compliance with these laws, regulations, and ordinances.

The product is very similar in composition and function to products currently produced at both Ortho facilities. These products have no negative impact on the ability of the Corporation to comply with emission standards. Approval of the application for Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets will not add to the emission rate at the facilities in a manner that will result in non-compliance.

Raritan Facility

Air emissions will not occur from production of this product. This is due to a closed air handling in which exhaust air from production is filtered and returned to the process systems rather than discharged to the environment. The air filtration system consists of a dust collector system with 99% removal efficiency, followed by two HEPA filters connected in series, each with 99.97% removal efficiency. The system filters particulates generated by addition of powdered ingredients in manufacturing the product. The filtered air is then returned to the process building. Collected particulates and filter media are disposed through high temperature incineration.

Water emissions are calculated to be parts per million (PPM) product in the effluent leaving the facility. This is based upon an expected loss of

kg of product in the washwater (% of batch weight), being mixed into the 70,000 gallon per day facility discharge. The amount that would reach the treatment plant would be parts per billion (PPB), based upon the treatment plant capacity of 20 million gallons per day.

Norgestimate is present in the product in concentrations of 0.25% and Ethinyl Estradiol is present in concentrations of 0.035%. The amount of the active in the wastewater at the facility discharge is PPB Norgestimate and PPB Ethinyl Estradiol. The amount at the sewerage plant would be PPB Norgestimate and PPB for Ethinyl Estradiol. Since neither Norgestimate nor Ethinyl Estradiol is regulated as an environmental pollutant, these levels in the emissions would not affect compliance at the Raritan facility.

Manati Facility

Air emissions will not occur from production of this product due to an air handling system very similar to that discussed above being in place at the Manati facility.

Water emissions are calculated to be PPM product in the effluent leaving the facility. This is based upon an expected loss of kg of product in the washwater, being mixed into the 15,000 gallon per day facility discharge. The amount that would reach the treatment plant would be PPB, based upon the treatment plant capacity of 8.3 million gallons per day.[2]

The amount of Norgestimate in the wastewater at the facility discharge would be PPB and the amount of the sewerage treatment plant would be

PPB. The amount of Ethinyl Estradiol in the wastewater at the facility discharge would be PPB and the amount at the sewerage treatment plant would be PPB. Since Norgestimate and Ethinyl estradiol are not regulated as environmental pollutants, these levels in the emissions would not affect compliance at the Manati Facility.

Consumer Use

Release of the material to the environment is not expected from use of the product. Since the material is completely consumed in the use, no emission of Norgestimate nor Ethinyl Estradiol should occur from use of the new product.

Disposal of Waste from Manufacturing and Use

The material requiring disposal would include returned goods and manufacturing waste. All waste materials will be disposed by high temperature incineration at Ortho Pharmaceutical Corporation's Raritan New Jersey facility or through contract vendors. Assuming a 10% ash content from destruction of the waste, 40 kg of ash will be generated for every batch or its equivalent incinerated. Based upon current practices with existing product, less than kg of ash per year will require disposal. The ash will consist of carbon and inorganic salts. The high temperatures of the incinerator (in excess of 1000 °F) would destroy the active ingredient, with the resultant ash presenting no expected environmental concerns.

Air emissions from incineration of the product are not expected to contain active ingredient. Tests on the emissions from the Ortho incinerator on other

products containing contraceptive steriods showed no steroid present at parts per trillion detection levels.[3]

7. Fate of Emitted substances in the Environment

As discussed in Section 6 of the Environmental Assessment, the environmental concentrations of the product are expected to be very low. The levels of Norgestimate and Ethinyl Estradiol in the environment through manufacture, use, and disposal of the product are expected to be virtually non-detectable in environment samples.

Raritan Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be parts per billion (PPB). The amount of Ethinyl Estradiol is calculated to be PPB. This is based upon the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 400.[1] No adverse impact is expected from this concentration.

Manati Facility

The amount of Norgestimate at the mixing zone of the wastewater treatment plant discharge is calculated to be PPB. The amount of Ethinyl Estradiol is calculated to be PPB. This is based on the assumption that the material passes through the treatment plant without treatment. It is also based on the mixing zone dilution of 1 to 375.[2] No adverse impact is expected from this concentration.

Emission form Use and Disposal

Emission of the product to the land is not expected due to disposal by high temperature incineration. The incineration of the product will destroy the material, with approximately 2 cubic yards of ash yearly resulting from the incineration. The ash will be inert and present no threat to the environment. Disposal of unused product by the consumer is expected to present minimal impact to the environment. The amount of material in the product package corresponds with the prescribed regimen of use, and thus the product should be consumed through use rather than be disposed in unused form. In addition, the expense of the product will encourage use rather than disposal.

Degradation in the Environment

The emission levels discussed above represent the maximum expected environmental concentrations of Norgestimate (PPB or mcg./liter of water). These levels assume no treatment or biodegradation in the environment. However, significant reductions of these levels should occur through biological degradation in the wastewater treatment plant and in the environment.

There is extensive literature on the biodegradation of steroidal compounds by naturally occurring microoganisms. These studies [4,5,6] show a wide variety of microbes that effectively metabolize and degrade steroids through side chain removal and ring cleavage. Soil and other environmentally occurring micro-organisms are responsible for this biodegradation and provide an

effective means to biodegrade any emitted active compound from manufacturing the new product.

The environment is additionally provided protection due to the metabolism of the active ingredients by higher organisms. Pharmacologic studies [7] on the actives show no unexpected metabolic products. As such, biological metabolism of Norgestimate and Ethinyl Estradiol should readily occur with the production of no adverse impacts to the environment.

8. Environmental Effects of Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets

The calculations for the emission of the new drug substance, Norgestimate, and the other active ingredient Ethinyl Estradiol, indicate that the maximum expected environmental concentrations will be very low. Manufacture of the product will not produce air emissions, and maximum water emissions are expected to be mcg./l of Norgestimate and mcg./l of Ethinyl Estradiol from either facility. Due to further dilution and biodegradation in the environment, the concentrations of Norgestimate and Ethinyl Estradiol in the ambient environment will be many orders of magnitude lower. A comparison of the toxicological data for Norgestimate plus Ethinyl Estradiol with the expected maximum environmental concentration of the actives indicates that no adverse environmental impacts are expected from the manufacture, use, and disposal of Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets.

Toxicological studies[7] for Norgestimate and Norgestimate plus Ethinyl Estradiol assessed the following:

1. Acute Toxicity;
2. Sub-chronic toxicity;
3. Chronic toxicity;
4. Reproductive effects and teratology;
5. Mutagenicity; and,
6. Carcinogenicity.

Acute Toxicity

The studies assessed the toxicity of Norgestimate and Norgestimate in combination with Ethinyl Estradiol (5:1) administered via the intravenous route. The species studied were mice, Long Evans rats, and beagle dogs. The (LD_{50}) for oral administration of Norgestimate and Norgestimate plus Ethinyl Estradiol (5:1) was greater than 5000 mg/kg. Since the maximum expected environmental concentration of the actives at the point of environmental release is mcg/l for Norgestimate and mcg/l for Ethinyl Estradiol, the acute toxic dose is billion times greater than the maximum expected environmental concentration of these compounds in one liter of water. It is virtually impossible for an acute toxic reaction to occur from environmental release of Norgestimate plus Ethinyl Estradiol.

Sub-Chronic Toxicity

Studies were done assessing the toxicity of sub-chronic doses of Norgestimate and Norgestimate plus Ethinyl Estradiol in female Long Evans

rats, female beagle dogs and female Rhesus monkeys. The doses were orally administered for three months as follows:

Rats - 0.5, 1.0, 2.5, or 10.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Rats - 0.55, 1.10, 2.75, or 11.0 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Dogs - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 0.15% agar suspension;

Dogs - 0.28, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10.1)/kg/day in 0.15% agar suspension;

Monkeys - 0.25, 1.5, or 5.0 mg Norgestimate/kg/day in 9.,5% carboxymethyl-cellulose suspension; and,

Monkeys - 0.275, 1.65, or 5.5 mg Norgestimate plus Ethinyl Estradiol (10:1)/kg/day in 0.5% carboxymethylcellulose suspensions.

The administration of Norgestimate and Norgestimate plus Ethinyl Estradiol in the dosage levels listed above resulted in physiological changes consistent with the activity of contraceptive steroids. Lower dosage levels resulted in less profound changes, and the studies noted no unexpected effects for the compound.

The lowest dosage level in the study, 0.25 mg/kg/day resulted in no unexpected adverse physiological impacts. This level is extremely large when compared with the maximum expected environmental concentrations of

Norgestimate and Ethinyl Estradiol. The 0.25 mg is approximately times greater than the maximum environmental levels of the actives. The levels in the environment are not expected to present any sub-chronic toxic effects.

Chronic Toxicity

Studies were conducted using female Long Evans rats, beagle dogs, and Rhesus monkeys for a period of one to two years. The doses were administered on a regimen that mimicked human use patterns using dosages of Norgestimate plus Ethinyl Estradiol in a 5:1 ratio.

The dosages in the rat studies ranged from 0.019 mg/kg/day to 3.0 mg/kg/day and represent 6.25 to 1000 times the strength of the human dose. Dosages in the dog and monkey studies ranged from 0.06 to 0.6 mg/kg/day, representing 20 to 200 times the strength of the human dose.

The administration of the compounds to the test subjects resulted in physiological changes expected from the pharmacologic effects of contraceptive steroids. The low and moderate dosage levels resulted in no significant changes while a significant response did occur only in the very high dosage level. The very high dosage (1000 times human dose) resulted in an increase of mammary gland adenocarcinomas of the rats. No increase in mammary gland adenocarcinomas was noted in all other dosage levels.

The lowest dosage level, 0.019 mg/kg/day, which resulted in no unexpected adverse reactions, represents a level times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol in

one liter of water. The highest dosage level in all tests, which represents the only dosage level which resulted in a significant adverse effect, increasing mammary gland adenocarcinoma, is more than million times larger than the maximum expected environmental concentrations of Norgestimate plus Ethinyl Estradiol in one liter of water. Based upon these observations, it is highly unlikely that the environmental releases of the actives from manufacturing or use will present chronic toxicity concerns.

Reproductive Effects and Teratology

Tests in female Long Evans rats indicated that administration of Norgestimate plus Ethinyl Estradiol (5:1) resulted in physiological changes consistent with administration of contraceptive steroids. The results indicate a dose response relationship directly correlated to the strength of the dose, with higher doses resulting in more profound effects.

Additionally, the tests indicated that the formulation did not produce teratogenic effects in the tested subjects. The tests did produce evidence of embryotoxicity in high dosage levels, but these embryotoxic effects did not occur in low dose levels.

The low dose levels in the studies, 0.03 mg/kg/day, produced physiological results consistent with those expected from administration of this class of compounds. No adverse effects were noted at the low dosage level, which is approximately times greater than the expected maximum environmental concentration of Norgestimate plus Ethinyl Estradiol. Environmental releases are not expected to result in adverse reproductive impacts.

Mutagenicity

Mutagenic potential for Norgestimate plus Ethinyl Estradiol (7:1) was assessed using in vitro (Ames tests) and in vivo (Sister Chromatic1 Exchange, Mouse Micronucleus test) methods. The tests showed no mutagenic potential for doses as high as 114 mg/kg in vivo. The levels assessed for mutagenic potential represent levels approximately million times greater than the maximum expected environmental concentrations of the substances. Environmental releases of Norgestimate plus Ethinyl Estradiol should present no mutagenic potential.

Carcinogenicity

As discussed in the section on chronic toxicity, mammary gland adenocarcinomas did occur in rats treated with very high doses of Norgestimate plus Ethinyl Estradiol. These levels represent 1000 times the expected therapeutic dose and million times the expected maximum environmental concentration of Norgestimate. Lower dose levels, also significantly higher than the expected therapeutic dose and expected maximum environmental concentration, showed no evidence of an increased risk of developing mammary gland adenocarcinomas. Long term studies in dogs (7 years) and monkeys (10 years) showed the occurrence of 1 leiomyosarcoma of the uterus in the dog at high dose level (25 times the therapeutic dose and times the expected maximum environmental concentrations) and 1 mucoepidermoid carcinoma of the cervix in the monkey at high dose level (50 times the therapeutic close and times the expected maximum environmental concentrations). These

changes are known to occur spontaneously and the test data suggest that these tumors may be spontaneous occurrences. It is highly improbable that environmental releases of Norgestimate will result in an increased incidence of these carcinomas. Environmental release of Norgestimate from manufacture, use, or disposal does not appear to present a carcinogenicity concern.

Effects on Plant Life

The toxicology data does not assess potential effect on plant life. The compounds are specific in their activity and are not expected to adversely affect plant life. In addition, the very low concentrations in the environment and the biodegradability of the materials would mitigate any potential for adverse effects on plant life.

Environmental Effects Summary

There appears to be very little potential for adverse environmental effects from releases of Norgestimate plus Ethinyl Estradiol. The combination of very low environmental concentrations, probable biodegradability, relatively low toxicity, and lack of mutagenic potential indicate that no adverse impacts should result from the manufacture, use, or disposal of Norgestimate plus Ethinyl Estradiol.

9. Use of Resources and Energy

The production of Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets will use processes and equipment presently used for similar products.

The production of the product will require a commitment of those materials, listed in section 5 for each batch of product manufactured. A commitment of fossil fuel will be required for production, transportation, and disposal of the product. No new land use commitments will be required for the manufacture of the product and a yearly land use commitment of less than 2 cubic yards of landfill space will be needed for the disposal of incinerator ash from incineration of the returned goods and off specification material. No adverse impacts are expected on endangered species nor registered historic places.

10. Mitigation Measures

No adverse impacts are anticipated from production, use, and disposal of Norgestimate 250 mcg. plus Ethinyl Estradiol 35 mcg. Tablets. All necessary pollution control measures are in place for production, use, and disposal of the product.

11. Alternatives to Proposed Action

No alternatives to the proposed action have been identified as necessary.

12. Preparer

Timothy McGuinness
Environmental Engineer
Ortho Pharmaceutical Corporation
Eight years of professional experience, five with the New Jersey Department of Environmental Protection and three with Ortho Pharmaceutical Corporation.
Bachelor degree in Microbiology plus graduate study in Chemical Engineering, Biochemistry and Microbiology.
Certified Hazardous Material Manager

13. Certification

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for preparation of the Environmental Assessment.

Date March 13, 1987

Signature [signature] FOR T. McGINNIS (METARCH)

Title Mgr of Project Engineering

14. References

1. Somerset Raritan Valley Sewerage Authority Industrial Pretreatment Program Technical Report; Metcalf and Eddy, Inc./Engineers, 1984.

2. Personal communication with Mr. Carl Axel Soderberg, Puerto Rico Environmental Quality Board.

3. Emissions evaluation of the Kelly Waste Incinerator Exhaust, Ortho Pharmaceutical Corporation; Betz, Converse, and Murdock Engineers Inc., 1982.

4. Mahato, S. and Mukherjee, A. Steroid Transformations by Microorganisms, Phytochemistry, Vol 23, No. 10, pp 2132-2154, 1984.

5. Kieslich, K. and Sebek, O.K. Microbial Transformation of Organic Compounds; Alkanes, Alicyclics, Terpenes, and Alkaloids. Annual Report on Fermentation Processes, 1:267-297, 1979.

6. Charney, W. and Herzog, H.L. Microbial Transformations of Steriods; a Handbook. Academic Press, New York 1969.

7. Complete information on Pharmacology and Toxicology contained elsewhere in the New Drug Application.

Ethinyl Estradiol
Common Name
Cat # 26000
Unit package size: 150 mg

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

address:
12601 Twinbrook Parkway
Rockville, MD 20852 USA

emergency and information
telephone calls:
(301) 881-0666

Jerome A. Halperin
Responsible Party

08-10-93
date prepared

WARNING STATEMENT
WARNING! REFERENCE STANDARD; NOT FOR HUMAN CONSUMPTION; AVOID INGESTION, INHALATION, SKIN CONTACT. FOR CHEMICAL TEST AND ASSAY USE ONLY.

SECTION 1 - IDENTITY

COMMON NAME	Ethinyl Estradiol
SYNONYMS	n/a
CAS NUMBER	57-63-6
RTECS NUMBER	RC8925000
CHEMICAL NAME	19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17alpha)-
CHEMICAL FAMILY	A Steroid
THERAPEUTIC CATEGORY	Estrogen
FORMULA	$C_{20}H_{24}O_2$

SECTION 2 - HAZARDOUS INGREDIENTS

	NAME	PERCENT	THRESHOLD LIMIT VALUE (UNITS)
PRINCIPAL HAZARDOUS COMPONENT(S)/[Chemical & Common name(s)]	Ethinyl Estradiol	Pure Material	Not Established

SECTION 3 - PHYSICAL AND CHEMICAL CHARACTERISTICS (Fire & Explosion Data)

MELTING POINT	182 - 184°C (the hydrated form melts at 141 - 146°C)
BOILING POINT	n/a
SPECIFIC GRAVITY (H_2O = 1)	n/a
VAPOR PRESSURE (mm Hg)	n/a
PERCENT VOLATILE BY VOLUME (%)	n/a
VAPOR DENSITY (AIR = 1)	n/a
EVAPORATION RATE	n/a

n/a = not applicable

MATERIAL SAFETY DATA SHEET
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SOLUBILITY IN WATER	Insoluble
REACTIVITY IN WATER	n/a
APPEARANCE AND ODOR	White to yellowish-white crystalline powder; odorless
FLASH POINT	n/a
FLAMMABLE LIMITS IN AIR % BY VOLUME	LOWER n/a UPPER n/a
EXTINGUISHER MEDIA	Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.
AUTO-IGNITION TEMPERATURE	n/a
SPECIAL FIRE FIGHTING PROCEDURES	As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE AND EXPLOSION HAZARDS	This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. When heated to decomposition material emits acrid smoke and irritating fumes. Emits toxic fumes under fire conditions.

SECTION 4 - PHYSICAL HAZARDS

STABILITY	( ) Unstable (X) Stable
CONDITIONS TO AVOID	Material is stable from a safety point of view. Avoid exposure to light.
INCOMPATIBILITY (MATERIALS TO AVOID)	Oxidizing agents and metals
HAZARDOUS DECOMPOSITION PRODUCTS	When heated to decomposition material emits acrid smoke and irritating fumes. Emits toxic fumes under fire conditions.
HAZARDOUS POLYMERIZATION	( ) May Occur (X) Will Not Occur

SECTION 5 - HEALTH HAZARDS

THRESHOLD LIMIT VALUE	None established
SIGNS AND SYMPTOMS OF OVEREXPOSURE	[Ethinyl Estradiol CAS RN: 57-63-6 TDLo: 21 mg/Kg/21D-Intermittent oral-woman; LD_{50}: 1200 mg/Kg oral-rat; LD_{50}: 471 mg/Kg intraperitoneal-rat; LD_{50}: >2 grams/Kg subcutaneous-rat;

n/a = not applicable

MATERIAL SAFETY DATA SHEET
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LD_{50}: 1737 mg/Kg oral-mouse;
LD_{50}: 250 mg/Kg intraperitoneal-mouse;
LD_{50}: >3 grams/Kg subcutaneous-mouse;
Mutagenicity Data [CCRIS] [RTECS];
Carcinogenicity Data [CCRIS] [RTECS];
Tumor Promotion Data [CCRIS];
Reproductive Effects Data [RTECS]!

The usual oral adult dose of ethinyl estradiol is 0.05 mg, one to three times a day; but for cancer treatment, much higher doses are used. Adverse effects include nausea, vomiting, abdominal cramps, bloating, yellow eyes or skin, involuntary muscle movements, skin irritation, headache, mild diarrhea, dizziness, change in weight, swelling of feet or lower legs, changes in sex drive, and loss of appetite. Women may develop fullness and tenderness of breasts, vaginal and uterine bleeding, increased hair growth and disturbance of menstrual cycle. Men may experience sudden loss of coordination, pain in chest, groin, or legs, shortness of breath, slurred speech, vision changes, numbness in extremities, breast enlargement, loss of sexual drive, sexual organ degeneration, and other feminizing effects. NOTE: Changes in secondary sexual characteristics are fully reversible on cessation of exposure. Possible allergic reaction to dust if inhaled, ingested or in contact with skin.

ACUTE: Eye, skin and/or respiratory tract irritation
CHRONIC: Possible hypersensitization and cancer

PRECAUTIONS TO CONSIDER

WARNING: This material is a possible human carcinogen. Persons developing hypersensitivity (anaphylactic) reactions must receive immediate medical attention. Extremely small amounts of this material are physiologically active and enough material can be absorbed through the skin or by the respiratory route to produce effects. Material may be irritating to mucous membranes and respiratory tract. Estrogens are not recommended for use during pregnancy because studies suggest an association of such usage with congenital malformations. (FDA Pregnancy Category X) [USP-DI 13th ed. 1993] As a general rule, when handling USP Reference Standards avoid all contact and inhalation of

n/a = not applicable

Ethinyl Estradiol
Common Name
Cat # 26000

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

dust, fumes, mist, and/or vapors associated with the material. Keep container tightly closed and use with adequate ventilation; wash thoroughly after handling. Individuals working with chemicals should consider all chemicals to be potentially hazardous even if their individual hazards may be uncharacterized or unknown.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE

Hypersensitivity to material, known or suspected breast cancer, known or suspected pregnancy, undiagnosed abnormal vaginal bleeding, endometriosis, gallbladder disease or gallstones, liver dysfunction, hypercalcemia associated with metastatic breast disease, jaundice, porphyria, uterine fibroids, cerebrovascular or coronary artery disease, active thrombophlebitis and/or thromboembolic disorders.

CHEMICAL LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN

NATIONAL TOXICOLOGY PROGRAM	Human:	Inadequate Evidence
	Animal:	Sufficient Evidence
I.A.R.C. Monographs	Human:	No Data Available
	Animal:	Sufficient Evidence

OSHA ( ) Yes (X) No

OTHER: Independent studies have shown an increased risk of endometrial cancer in postmenopausal women treated with estrogens for prolonged periods. The risk of endometrial cancer in estrogen users, which appears to depend on duration of treatment and dose, was 5 to 10 times greater than in non-users. However, this issue remains unresolved. In certain animal species, long-term, continuous administration of estrogens increases the frequency of cancer of the breast, cervix, vagina, and liver. Estrogens have been reported to be associated with carcinoma of the male breast. Males treated with estrogens should have regular breast examinations.

[USP DI 13th ed. 1993]

ACGIH TLV:	n/a	OTHER EXPOSURE LIMIT(S) USED:	n/a

n/a = not applicable

Ethinyl Estradiol
Common Name
Cat # 25000

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

OSHA PERMISSIBLE EXPOSURE LIMIT:	Not established
OTHER EXPOSURE LIMIT USED	Not established
EMERGENCY AND FIRST AID PROCEDURES	Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention. Single large overdoses of estrogens, even in small children, have not been reported to cause serious effects; however, such overdose victims should receive medical attention as a precaution. Nausea is common and withdrawal bleeding in females may occur as a result of overdose. [USP DI 9th ed. 1989]
1. INHALATION	May cause irritation of respiratory tract. Avoid inhalation. Remove to fresh air.
2. EYES	May cause irritation. Flush with copious quantities of water.
3. SKIN	May cause irritation. Avoid contact. Flush with copious quantities of water.
4. INGESTION	May cause irritation. Flush out mouth with water. This material is rapidly absorbed from the gastrointestinal tract.

SECTION 6 - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (SPECIFY TYPE)	NIOSH approved respirator
VENTILATION	Adequate
LOCAL EXHAUST	Recommended
MECHANICAL (GENERAL)	Recommended
OTHER	n/a
PROTECTIVE GLOVES	Rubber
EYE PROTECTION	Safety goggles
OTHER PROTECTIVE CLOTHING OR EQUIPMENT	Head cover, coverall or laboratory coat buttoned to neck, long sleeves; protect exposed skin.

n/a = not applicable

Ethinyl Estradiol
Common Name
Cat # 26009

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

SECTION 7 - SPECIAL PRECAUTIONS AND SPILL/LEAK PROCEDURES

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE	Store in tight, light-resistant container as defined in the United States Pharmacopeia. This material should be handled and stored per label and other instructions to ensure product integrity. Because extremely small doses of this material are physiologically active, toxic manifestations during laboratory use are possible, especially if adequate safeguards are not observed.
OTHER PRECAUTIONS	Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control. Wash thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before reuse. Do not permit eating, drinking or smoking near material.
STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED	Wear approved respirator and chemically compatible gloves. Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.
WASTE DISPOSAL METHODS	Dispose of waste in accordance with all applicable Federal, State and local laws.

NOTICE: The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not relate to any other use of the substance described. Its use is intended by persons having technical skill and at their own discretion and risk. The information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

ATTENTION:

This Product is Sold as a Reference Standard for Use In Chemical Analysis Not For Human Consumption.

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n/a = not applicable

ROUSSEL UCLAF

NORGESTIMATE

S A F E T Y

D A T A S H E E T

NN : 3065

NFI :

Date of issue : 12/10/89
Date of revision : 25/03/93
VERSION :

NOTA : THE LATEST PERTINENT MODIFICATIONS INTRODUCED IN THE SAFETY DATA SHEET ARE SIGNALIZED BY A LETTER PLACED IN FRONT OF THE CONCERNED HEADING

INDUSTRIAL HYGIENE DELEGATION TEL : 49-91-44-31 FAX : 49-91-48-80

1. IDENTIFICATION of the SUBSTANCE/PREPARATION and the COMPANY

1.1. Identification of the substance or preparation

TRADE NAME	: NORGESTIMATE
SYNONYMS	: RU 23147 NORGESTERAL acetate oxime
CHEMICAL NAME	: (+)-13-ethyl-3-hydroxyimino-18,19-dinor-17alpha-preg-4-en-20-yn-17beta-yl acetate.
CAS NUMBER	: 35189-28-7
EINECS NUMBER	:
CHEMICAL FAMILY	: Hormone
FORMULA	: C23 H31 N O3
MOLECULAR MASS	: 369.5
KIND OF USE	: Medical use
PRODUCT CODE	:

1.2. Company / Undertaking identification

SUPPLIER	: ROUSSEL UCLAF
ADDRESS	: 35, Bd des Invalides; 75007 PARIS - FRANCE; Tel : 40-62-40-62

1.3. EMERGENCY PHONE NUMBER

2. COMPOSITION/INFORMATION on INGREDIENTS

HAZARDOUS CONSTITUENTS	:
IMPURITIES	:

3. HAZARDS IDENTIFICATION

HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

4. FIRST-AID MEASURES

CONTACT WITH SKIN: Rinse with plenty of water
CONTACT WITH EYES : Rinse immediately with plenty of water for at least 15 minutes
IN CASE OF INHALATION : Make the victim blow his nose
IN CASE OF INGESTION : Do not make the victim vomit Alert a physician

5. FIRE-FIGHTING MEASURES

SUITABLE EXTINGUISHING MEDIA	: usual means
UNSUITABLE EXTINGUISHING MEDIA	: Jet of water from a fire hose
FIRE AND EXPLOSION HAZARDS	: In case of fire, the product emits toxic fumes
SPECIAL PROTECTIVE EQUIPMENT	: Wear a self-contained respiratory apparatus
OTHER RECOMMENDATIONS	: Avoid rejection of extinguishing water in the environment

6. ACCIDENTAL RELEASE MEASURES

Collect thoroughly into a plastic bag Rinse the polluted area with plenty of water

7 HANDLING AND STORAGE

7.1 HANDLING

TECHNICAL MEASURES	: Mechanical sucking ventilation at source of formation of dust

SPECIAL PROTECTION MEASURES ..... :shower at end of work.

7.2 STORAGE

SENSIBILY TO DAMP ..... :Not observed.
SENSIBILY TO LIGHT ..... :Not observed.
SENSIBILY TO OXIDATION ..... :Not observed.
SPECIAL STORAGE REQUIREMENTS ..... :Room temperature (<36 F)
LOW TEMPERATURE TO BE AVOIDED .... :
STORAGE CONDITIONS ..... :Room temperature (T<= 30°C) protected from light
SHELF LIFE ..... :5 years.
STORAGE FACILITIES ..... :Noxious products.
RECOMMENDED PACKAGING MATERIAL ... :Glass, polythene.
SUPPLIER PACKAGING ..... :GLASS, POLYTHENE
PACKAGING MATERIAL TO BE AVOID ... :Unknown.
INCOMPATIBLE SUBSTANCES ..... :Unknown.
OTHERS RECOMMENDATIONS ..... :None.

8. EXPLOSURE CONTROLS/PERSONAL PROTECTION

PERSONAL PROTECTION/WORKSHOP ..... :Wear suitable gloves, safety goggles, and dust respirator
PERSONAL PROTECT/LABORATORY ..... :Wear suitable gloves, safety goggles, and dust respirator

STEL .....:NO
TWA .....:NO
OLFACTORY THRESHOLD .....:NO
IDLH .....:

DETECTION ..... :

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE ..... :Powder (practically white)
PH ..... :Not concerned.
CHARACTERISTIC TEMPERATURES ..... :Melting point : 222 -228°C
FLASH POINT ..... :Not applicable.
AUTOFLAMMABILITY ..... :Not determined.
INFLAMMABILITY LIMITS ..... :NO
EXPLOSIVE PROPERTIES/KST ..... :
MINIMUM INFLAMMATION ENERGY ..... :
COMMENTS ON FLAMMABILITY ..... :
VAPOUR PRESSURE ..... :Not determined.
RELATIVE DENSITY ..... :Not determined.
SOLUBILITY ..... :Insoluble in water Soluble in : chlorinated solvents.
Sparingly soluble in methano.
PARTITION COEFF. OCTANOL/WATER ... :
VAPOUR/AIR DENSITY ..... :
OTHERS DATA ..... :Alpha D20 : +40 - +46°(C,5%,ch.oroform)

10. STABILITY AND REACTIVITY

HAZARDOUS REACTIONS ..... :None to our knowledge
HAZARDOUS DECOMPOSIT. PRODUCTS ... :Unknown.
SENSITIVITY TO JOLTING ..... :
PRODUCTS OF DECOMPOSITION
HEAT STABILITY ..... :

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY	:LD 50 oral route/rat ; > 2000 mg/kg
IRRITANT POTENTIAL	:Cutaneous irritation (rabbit) : not irritant
PHYSIOLOGICAL ACTIVITY	:Substance physiologically active at low dose oral contraceptive (in association with ethinyl estradiol).
TERATO/MUTA/CARCINOGENICITY	:
COMMENTS/SYMPTOMS	:HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
OTHER RECOMMANDATIONS	:

12. ECOLOGICAL INFORMATION

Biodegradable in natural media

13. DISPOSAL CONSIDERATIONS

NEUTRALIZATION OF THE PRODUCT	:Set in specialized and approved recuperator service
DESTRUCTION SOILED PACKAGING	:Set in specialized and approved recuperator service

14. TRANSPORT INFORMATION

TRANSPORT ASSIMILATION	:
SPECIAL PRECAUTIONS	:
CNU	:28*1
RTMD (FRANCE)	:6.1,90°c,6.1A,2811,60 .
RID/ADR	:6.1,90°c,6.1A,2811,60
OMCI/IMDG	:6.1,gr III,p6236,6 nocif
IATA	:6.1,gr III,,6 nocif
CARGO	:619 (100 kg)
PASSENGERS	:619 (200 kg)

15. REGULATORY INFORMATION

LABELLING (EEC NUMBER)	:Labelling according to EEC regulations
SYMBOLS	:Xn
PHRASES	:R20/21/22 S7-15
SPECIAL RISKS	:HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
SAFETY ADVICES	:Keep container tightly closed . Keep away from heat.
ADDITIONNAL LABELLING	:Room temperature (<86 F)
CANCER LIST	:

16. OTHER INFORMATION

None.

The information given in this sheet has been introduced in accordance with the guidelines established by article 10 of EEC directive 88/379, dated March 5,1991. This data sheet complement the user's instructions, but does not replace them. The information it contains is based on the knowledge available about the product concerned at the time it was compiled. Users are further reminded of the possible risks of using a product for purposes other then those for which it was intended. The required information complies with current EEC legislation; Adresses are requested to apply any additional national requirements.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum
CONSULTATION

Date · June 3, 1996

From Ridgely C. Bennett, M.D., M.P.H., HFD-510 Ridgely C. Bennett
P.C/mm 96.06.03

Subject Your Request to Review NDA 20-681 from a Safety Perspective

To Kevin D. White, HFD-540

I have reviewed volumes 1.1, 1.2, 1.4, 1.6, 1.13, 1.15, 1.20, and 1.22 of the original submission of NDA 20-681, Ortho Tri-Cyclen Tablets, a Type 6 New Drug Application.

Ortho Tri-Cyclen Tablets are currently approved under NDA 19-697 for the indication prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. NDA 20-681 supports the additional indication for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptives.

NDA 20-681 contains only clinical and statistical data to support the acne indication. The dosage regimen is exactly the same as that approved for contraception. No pharmacology, toxicology, ADME, human pharmacokinetics, chemistry, manufacturing, or control information is submitted in the NDA.

safety of Ortho Tri-Cyclen in healthy females has been established and documented in rious clinical trials as well as marketed use as a contraceptive in the United States and nine other countries.

NDA 20-681 contains data from two clinical trials supporting treatment of moderate acne vulgaris in females. The adverse reaction profile from these two trials is consistent with that found in previous contraceptive studies and are the known risks associated with oral contraceptives. Although the discontinuation rate due to adverse events was higher in the treatment group than the placebo group (18 subjects vs 9 subjects), most of the adverse events are known side effects of Ortho Tri-Cyclen and none of the discontinuations raised new safety concerns. Many of the adverse events were gastrointestinal symptoms.

A total of six subjects (out of 462) reported serious adverse events, three in the treatment group and three in the placebo group. The events did not follow any apparent pattern. There was one report each of throat constriction, breast carcinoma, and rectal bleeding in the treatment group.

In conclusion, the safety profile seen in the acne studies is consistent with the profile previously observed in oral contraceptive clinical studies and marketing experience.

Concur - Memo 6/4/96

Concur 6/5/96

cc: Arch NDA 20-681
HFD-540
HFD-510/Consults
HFD-510/Legalless

Department of Health and Human Services
Public Health Service
Food and Drug Administration

M E M O R A N D U M

Date: December 13, 1996

From: Division of Reproductive and Urologic Drug Products, HFD-580

Subject: Consult Request

To: Division of Dermatologic & Dental Drug Products, HFD-540

As you know from our previous telefacsimile, November 27, 1996, the Division of Reproductive and Urologic Drug Products has had the opportunity to briefly review the proposed labeling for Ortho Tri-Cyclen tablets (norgestimate/ethinyl estradiol) which adds the indication for the treatment of moderate acne vulgaris in females to the approved oral contraceptive labeling.

On initial review, the following modifications are recommended:

Physician Package Insert:

(1) Page 3: We recommend revision of the wording for the new indication to include a statement that women using this product need also be clearly alerted that this product prevents pregnancy. Advertising for this indication should clearly note the contraceptive properties. We thus recommend the sentence to read:

The sponsor may have additional wording suggestions that would incorporate this concept.

(2) Page 22: We recommend removing the words

in the new section of additional instructions for use in acne. As you know, oral contraceptives do interfere with the normal cycle. Although attempting to mimic a standard menstrual pattern, the "normal" or "natural" cycle is obliterated.

Thank you for the opportunity to participate in this review. We hope these comments were helpful in your review and action on this application. If further comments are generated by the formal Medical Officer Review we will convey them when available.

12/13/96

Lisa Rarick, M.D.
Director, DRUDP, HFD-580

cc:
HFD-580/Consult
HFD-580/Ckish/RBennett/HJolson/LPauls

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

JAC
FEB 5 1996

NDA 19-653/S-012
NDA 19-697/S-005

FEB 0 :

R.W. Johnson Pharmaceutical Research Institute
Attention: Ms. Isabel B. Drzewiecki
Senior Director, Regulatory Affairs
Route 202, P.O. Box 300
RARITAN NJ 08869-0602

JAN 2 9 1996

Dear Ms. Drzewiecki:

Reference is made to your November 3, 1994, supplemental new drug applications, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following preparations:

ORTHO-CYCLEN (NDA 19-653) AND
ORTHO TRI-CYCLEN (NDA 19-697)
(norgestimate/ethinyl estradiol) Tablets.

We also refer to your amendments dated November 30, 1995.

The supplemental new drug applications provide for a revised statement in the CLINICAL PHARMACOLOGY section regarding receptor binding studies, additions to the PRECAUTIONS section of additional drug interactions with laboratory tests, as well as an expanded statement regarding triglycerides and drug interactions with laboratory tests. These supplements also provide for additional references to the REFERENCE section of thephysician package insert.

We have completed the review of the draft labeling in these supplemnental applications as amended, and the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling. Marketing the product with the changes provided in these supplemental applications with FPL that is not identical to this draft labeling may render the products misbranded and unapproved new drugs. In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submissions please provide a highlighted or marked up copies that show the changes that are being made.

Please submit twenty copies of the FPL as soon as it is availabel. Please individually mount twelve of the copies on heavy weight paper or similar material. For administrative purposes, these submissions shuld be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 19-653/S-012 and 19-697/S-005. Approval of this FPL is not required before it is used.

Should additional information relating to the safety and effectiveness of these drugs become available, revision of the labeling may be required.

We remind you that you must comply with the requirements set forth under21 CFR 314.80 and 314.81 for an approved NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 443-3520.

Sincerely yours,

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

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

DEC 26 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 2145
12420 Parklawn Drive
Rockville, MD 20857

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Dear Sir/Madam:

Pursuant to the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act and Title 21 of the Code of Federal Regulations, 21 CFR 314.50, we are submitting a Type 6 New Drug Application for ORTHO TRI-CYCLEN Tablets. This application has been pre-assigned NDA 20-681.

ORTHO TRI-CYCLEN Tablets are approved under NDA 19-697 for the indication prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. This application supports the additional indication for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy.

This NDA has been prepared in accordance with 21 CFR 314.50, 21 CFR 314.54, FDA guidelines, and agreements made at our September 25, 1995 pre-NDA meeting. Since ORTHO TRI-CYCLEN Tablets are an approved product, this application contains only clinical and statistical data to support the acne indications. No Pharmacology/Toxicology, ADME (Item 5) , Human Pharmacokinetics (Item 6) information is included. Additionally, since no changes are being made to the manufacture of the currently approved drug product, no Chemistry, Manufacturing and Control information (Item 3) is being provided. An explanation of the organization of this NDA is located in the Overall NDA Reviewer's Guide contained in Volume 1.1.

In accordance with my October 10, 1995 telephone conversation with Mr. Tom Hassall, Consumer Safety Officer, CDER, the User Fee cover sheet for this submission indicates in the exclusion section that this is a Type 6 NDA. The required user fee of was sent under separate cover to the Mellon Bank, Pittsburgh, PA on December 18, 1995 (User Fee ID #2911).

Should you have any questions concerning this application, please contact me directly at (908) 704-4775 or at our new phone number dedicated for FDA use: (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Stephenie Barba
Director
Regulatory Affairs

SB:gg

Desk Copy: Lisa Stockbridge, CSO, Division of Metabolism and Endocrine Drug Products, Volume 1.1

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ORIGINAL
NEW CORRESP
NC

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

APR 2 6 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

FOUR MONTH SAFETY UPDATE

Dear Sir/Madam:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets for the additional indication for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy which was submitted on December 26, 1995. At this time, in accordance with 21 CFR 314.50 (d)(5)(vi)(b), we wish to submit our first Safety Update Report to the pending NDA.

Full reports for the two completed clinical studies conducted to support the additional indication were included in the original NDA. No clinical studies of ORTHO TRI-CYCLEN Tablets for this indication are ongoing. There is no new safety information available which would affect the conclusions or package insert statements as contained in the original NDA.

Should you have any questions, please contact me directly at (908) 704-4282 or our phone number dedicated for FDA use at (908) 704-4600.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 2 9 1996
HFD-

Sincerely,

Lewis Gryziewicz
Manager
Regulatory Affairs

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

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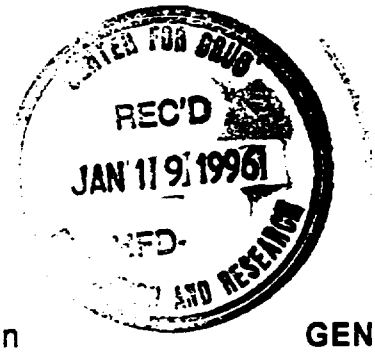

JAN 17 19

Kevin Darryl White
Food and Drug Administration
Division of Dermatologic and Ophthalmologic
Drug Products - HFD 540
Attn: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

GENERAL CORRESPONDENCE

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Dear Mr. White:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYCLEN Tablets for the indication for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy. Reference is also made to our January 16, 1996 telephone conversation during which you requested that we review the FDA 45 Day Meeting Checklist, copy attached, and forward our review to your attention.

As requested, attached are our responses to each of the items listed in the checklist. The submission is formatted with the question from the checklist stated followed by the response.

This NDA has been prepared in accordance with 21 CFR 314.50, 21 CFR 314.54, FDA guidelines, and agreements made at our September 25, 1995 pe-NDA meeting. Since ORTHO TRI-CYCLEN Tablets are an approved product, this application contains only clinical and statistical data to support the acne indications. No Pharmacology/Toxicology, ADME (Item 5), Human Pharmacokinetics (Item 6) information is included. Additionally, since no changes are being made to the manufacture of the currently approved drug product, no Chemistry, Manufacturing and Control information (Item 3) is being provided. An explanation of the organization of this NDA is located in the Overall NDA Reviewer's Guide contained in Volume 1.1 of the NDA.

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Should you have any questions, please contact me directly at (908) 704-4282 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Lewis Gryziewicz
Manager
Regulatory Affairs

LG:gg
Attachments

N:\GRYZIEW\5DYCHCK

ORIGINAL

AMENDMENT

BC

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

JAN 24 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Ophthalmologic
Drug Products - HFD 540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Blvd.
Rockville, Maryland 20850

GENERAL CORRESPONDENCE

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Dear Sir/Madam:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYCLEN Tablets for the treatment of moderate acne vulgaris in women who have no known contraindications to oral contraceptive therapy. Reference is also made to a telephone conversation between Mr. Kevin Darryl White, CSO, Division of Dermatologic and Ophthalmologic Drug Products (DDODP) and myself on January 17, 1996 during which Mr. White requested that the Environmental Assessment for our approved NDA 19-697 for ORTHO TRI-CYCLEN Tablets for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception be submitted to NDA 20-681.

As requested, please find enclosed copies of the Environmental Assessments for the 180/35 mcg and 215/35 mcg dose of Norgestimate/Ethinyl Estradiol Tablets which were originally provided in NDA 19-697 for ORTHO TRI-CYCLEN Tablets filed July 20, 1987, and for the 250/35 mcg Norgestimate/Ethinyl Estradiol Tablets provided in NDA 19-653 for ORTHO-CYCLEN® Tablets which was filed March 24, 1987 and incorporated into NDA 19-697 by cross-reference. The attachment details the changes to the original Environmental Assessment to reflect current practice at the manufacturing facilities.

NDA 20-681 provides for a new indication for ORTHO TRI-CYCLEN Tablets which is an approved product under NDA 19-697. There have been no changes to the Chemistry, Manufacturing, and Controls information for ORTHO TRI-CYCLEN Tablets.

As discussed at our September 25, 1995 pre-NDA meeting, this NDA contains only clincial and statistical data to support the acne indication. Once DDODP reviews this application, it will be withdrawn, and a labeling supplement to incorporate the new indication into the labeling will be submitted to NDA 19-697 with the Division of Metabolism and Endocrine Drug Products. It was agreed at the pre-NDA meeting that no Chemistry, Manufacturing, and Controls information would be required for approval of this NDA.

Should you have any questions, please contact me directly at (908) 704-4282 or our new number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Lewis Gryziewicz
Manager
Regulatory Affairs

LG:lf

enclosure

Desk Copy: Kevin Darryl White, CSO, DDODP

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

MAR 15 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

GENERAL CORRESPONDENCE

Dear Sir/Madam:

Reference is made to our pending New Drug Application 20-681, ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets. Reference is also made to a March 5, 1996 telephone conversation between Mr. Kevin Darryl White, Project Manager, FDA Division of Dermatologic and Dental Drug Products and Mr. Lewis Gryziewicz of the R.W. Johnson Pharmaceutical Research Institute during which Mr. White requested our evaluation of the risk of idiopathic cardiac death and/or fatal thromboembolism associated with third generation progestogens.

On January 26, 1996 our United Kingdom affiliate, Cilag Ltd., submitted the attached document in response to a request from the European Agency for the Evaluation of Medicinal Products (EMEA) and the Committee for Proprietary Medical Products (CPMP). On January 30, 1996 we submitted the same report to our approved New Drug Applications for our norgestimate containing oral contraceptives, NDA 19-653, ORTHO-CYCLEN® (norgestimate/ethinyl estradiol) Tablets and NDA 19-697, ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets. At this time we wish to submit this report to NDA 20-681.

During our telephone conversation, Mr. White referenced an article by Herschel Jick, et al in the December 14, 1995 Lancet, "Risk of Idiopathic Cardiovascular Death and Nonfatal Venous Thromboembolism in Women Using Oral Contraceptives With Different Progestagen Components". Please note that the Jick article discusses the risk associated with the use of desogestrel and gestodene containing oral contraceptives. In light of this information and corrorborating data from other studies we have revised our labeling for our approved desogestrel-containing oral contraceptive ORTHO-CEPT® (desogestrel/ethinyl estradiol) Tablets, NDA 20-301, to inform of a two-fold increase in the risk of venous thromboemolic disease as compared to other low-dose oral contraceptives.

MAR 15 1996

The Jick article does not discuss norgestimate-containing oral contraceptives. Norgestimate containing oral contraceptives should be considered as distinct entities and not grouped with other oral contraceptives based solely on their timing of introduction into the marketplace.

Also included in this submission is a report which we received fro Planned Parenthood Federation of America, Inc. discussing their evaluation of risk of thromboembolism and oral contraceptives. This information will also be submitted to NDA 19-653, NDA 19-697, and NDA 20-301.

We trust that the attached report answers any questions you may have concerning norgestimate-containing oral contraceptives. Should you have any questions, please contact me directly at (908) 704-4547 or at our new phone number dedicated for FDA use (908) 704-4600.

Very truly yours,

I. B. Drzewiecki

Isabel B. Drzewiecki
Senior Director
Regulatory Affairs

IBD:gg
Enc.

cc: Dr. Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Desk Copy: Mr. Kevin Darryl White, Project Manager
Division of Dermatologic and Dental Drug Products

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DUPLICATE
NEW CORRESP
NO

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

APR 12 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

GENERAL CORRESPONDENCE

Dear Sir/Madam:

Reference is made to our pending New Drug Application 20-681, ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets. Reference is also made to our March 15, 1996 submission of data on the safety of norgestimate-containing products to NDA 20-681 which included a copy of our U.K. affiliate's submission to the European Medicines Evaluation Agency (EMEA) and the Committee for Proprietary Medicinal Products (CPMP).

At this time, we are providing an update submitted to the EMEA on March 28, 1996 by our U.K. affiliate. This submission provides a reduction in total cycles from 342,348 to 306,844 for the open-label, non-randomized study performed in Germany. This information is being submitted under separate cover to our approved New Drug Applications for our norgestimate-containing oral contraceptives, NDA 19-653, ORTHO-CYCLEN® (norgestimate/ethinyl estradiol) Tablets and NDA 19-697, ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets.

Should you have any questions, please contact me directly at (908) 704-4282 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

Lewis Gryziewicz
Manager
Regulatory Affairs

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

OCT 07 1996

NEW CORRESPONDENCE

Kevin Darryl White
Project Management
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Mr. White:

Further to our telephone conversation of this morning, October 7, 1996, please find enclosed a disk in WordPerfect 6.0 format of the draft labeling for the ORTHO TRI-CYCLEN® acne indication. A copy of the labeling from the disk is consistent with the orginal labeling submitted on December 26, 1995 in New Drug Application 20-681.

Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

REVIEWS COMPLETED
DSC ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
DSC INITIALS DATE

RECD
OCT 09 1996
HFD
EVALUATION AND RESEARCH

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DOCUMENT

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

OCT 23 1996

RL

Ella Toombs, M.D.
Medical Reviewer
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

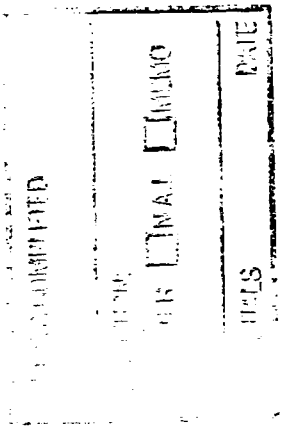
Dear Dr. Toombs:

In response to your request of October 21, 1996, to revise the draft labeling for the acne indication submitted on December 26, 1995 in New Drug Application 20-681 for ORTHO TRI-CYCLEN® Tablets (norgestimate/ethinyl estradiol), please find the attached pages which address each of the three points. Revisions have been made to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION sections of the Physicians' Package Insert. Only the revised portions of these sections are attached. A description of the changes are provided below.

Section: CLINICAL PHARMACOLOGY

FDA Comment: The draft labeling appears to link to strongly the emergence of facial acne with the drug's proposed mechanism of action.

PRI Response: Our response is provided in two parts. First, the CLINICAL PHARMACOLOGY section of the oral contraceptive labeling for ORTHO TRI-CYCLEN Tablets has been revised. This proposed revision was submitted on November 4, 1994 as supplemental application S-005 to NDA 19-697 (ORTHO TRI-CYCLEN Tablets, oral contraceptive indication). This was prior to submission of NDA 20-681 for the acne indication. Supplement S-005 was approved on January 29, 1996. I regret that we did not amend the draft acne labeling subsequent to receiving the approval letter from FDA. Attached behind the revised labeling is a copy of the November 4, 1994 letter, a November 30, 1995 amendment to the pending labeling supplement, and the Agency's approval letter of January 29, 1996. The supplement added a paragraph to the CLINICAL PHARMACOLOGY section on the components' effects on the sex hormone binging globulin (SHBG) and serum testosterone.



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OCT 23 1996

Second, this comment has been incorporated verbatim in a revised draft CLINICAL PHARMACOLOGY section for the acne indication. Because acne is of multifactorial etiology, the association between the noted effects on SHBG and testosterone and the drug product's effect on facial acne has been softened.

Section: INDICATIONS AND USAGE

FDA Comment: The description of the clinical studies for the acne indication should include the duration of the trials.

PRI Response: The first sentence of the third paragraph following Table I has been revised to indicate that the studies were of six months duration.

Section: DOSAGE AND ADMINISTRATION

FDA Comment: Specific guidance for the use of ORTHO TRI-CYCLEN for the treatment of facial acne should be provided.

PRI Response: The protocol for the two clinical studies for the acne indication provided a dosing regimen identical to the approved oral contraceptive regimen; i.e., 21 days of active medication followed by 7 days of placebo or no medication. Because of this, the draft labeling submitted with NDA 20-681, did not provide a separate DOSAGE AND ADMINISTRATION section for use in treating acne.

This section has been revised in two ways. First, the introductory sentence has been revised to note the product's use in treating acne. And second, following the introductory paragraph are four successive subsections which provide dosing recommendations for women who choose a 21 or 28 day regimen and a "Day 1 Start" or a "Sunday Start". Each of these four subsections has been revised in an identical fashion in the instructions to women who need to use a back-up method of birth control because of missed tablets to indicate that these instructions are specific for women using the product for oral contraceptive use only.

OCT 2 3 1996

Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681 and specifically the draft labeling, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

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

NOV 03 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

LABELING SUPPLEMENT

NDA 19-653
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please cross-refer to:

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

Dear Dr. Sobel:

Reference is made to our approved New Drug Applications 19-653 and 19-697 for ORTHO-CYCLEN Tablets and ORTHO TRI-CYCLEN Tablets, respectively and specifically to the Physicians' Package Insert and Detailed Patient Labeling for these oral contraceptive tablet products.

Pursuant to 21 CFR 314.70(b)(3), we wish to propose changes to the "CLINICAL PHARMACOLOGY," "PRECAUTIONS" AND "NON-CONTRACEPTIVE HEALTH BENEFITS" sections of the Physicians' Package Insert and the "HEALTH BENEFITS FROM ORAL CONTRACEPTIVES" section of the Detailed Patient Labeling. The proposed revisions are as follows:

Physicians' Package Insert

1. In the "CLINICAL PHARMACOLOGY" section of the insert we propose adding the following after the current first paragraph:

2. In the "PRECAUTIONS" section under subheading "8. INTERACTIONS WITH LABORATORY TESTS" we propose changing line "d." as follows:

   From: "d.

   To: "d.

3. In the "PRECAUTIONS" section under the subheading "8. INTERACTIONS WITH LABORATORY TESTS" we propose changing line "e." as follows:

   From: "e.

   To: "e.

4. The "REFERENCES" section of the current inserts will be revised to include references 90, 91, 92, 93 and 94 as outlined in Point 1.

5. Under "NON-CONTRACEPTIVE HEALTH BENEFITS" section of the insert we propose adding the following:

Detailed Patient Labeling

In the "HEALTH BENEFITS FROM ORAL CONTRACEPTIVES" section we propose adding the following:

In support of this supplement we have included reprints from the scientific literature, including a review of the available literature on the effects of oral contraceptives on bone, which substantiate each proposed change. This review and the literature to support the addition of "decreased risk of bone loss" to the "Non-Contraceptive Health Benefits" may be found in Volume 2 of 2. Articles to support the other revisions may be found in Volume 1 of 2. To facilitate your review, we have included a summary of proposed labeling changes and annotated Physicians' Package Insert and Detailed Patient Labeling. Furthermore, we have also appended a completed Form FDA 356h and four copies, in draft form, of the Physicians' Package Insert and Detailed Patient Labeling which have been revised as cited above.

Should you have any questions, please contact Mr. Joseph Carrado at (908) 704-4812.

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

I. B. Drzewiecki

Isabel B. Drzewiecki
Senior Director
Regulatory Affairs

IBD/cmw

Enclosures

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THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
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NOV 30 1995

Solomon Sobel, M.D.
Food and Drug Administration
Division of Drug Metabolism and
Endocrine Drug Products
Center for Drug Evaluation & Research
HFD #510
DOCUMENT CONTROL RM#14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 19-653
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please cross-refer to:

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

LABELING SUPPLEMENT AMENDMENT

Dear Dr. Sobel:

Reference is made to our approved New Drug Applications 19-653 and 19-697 for ORTHO-CYCLEN Tablets and ORTHO TRI-CYCLEN Tablets, respectively, and more specifically to our November 3, 1994 supplements (Supplement 012 for ORTHO-CYCLEN Tablets; Supplement 005 for ORTHO TRI-CYCLEN Tablets) which proposed changes to the Physicians Package Insert and Detailed Patient Labeling for these oral contraceptive products.

At this time we wish to amend these labeling supplements by deleting the following two proposals (one from the Physicians' Package Insert and one from the Detailed Patient Labeling):

Physicians' Package Insert

5. Under "NON-CONTRACEPTIVE HEALTH BENEFITS" section of the insert we had proposed adding the following:

Detailed Patient Labeling

In the "HEALTH BENEFITS FROM ORAL CONTRACEPTIVES" section we had proposed adding the following:

We now request that these two items be deleted but we still wish, however, to incorporate the remaining proposals, noted as points 1 to 4 under "Physicians' Package Insert", in our November 3, 1994 submission (copy attached).

If you have any questions please contact me at our phone number designated for FDA use only, (908) 704-4600 or if you prefer you may contact me directly at (908) 704-4812.

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

Joesph A. Carrado, M.Sc., R.Ph.
Associate Director
Regulatory Affairs

c: Dr. L. Stockbridge (HFD 510)

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ORIGINAL
NEW CORRESP
NC

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

October 29, 1996

Ella Toombs, M.D.
Medical Reviewer
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Dr. Toombs:

In response to your request of October 28, 1996, to revise the draft labeling for the acne indication submitted on October 23, 1996 to New Drug Application 20-681 for ORTHO TRI-CYCLEN® Tablets (norgestimate/ethinyl estradiol), please find the attached pages which address the two points discussed in our conversation. Revisions have been made to the CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION sections of the Physicians' Package Insert. The revised portions of these sections are attached. A description of the changes are provided below.

Section: CLINICAL PHARMACOLOGY

FDA Comment: FDA requested that we delete the phrase in the description of acne in the first sentence. FDA also suggested clarifying language for the remaining sentences in the October 23rd draft. The proposed sentence is the following.

PRI Response: The revisions requested by the Agency have been made.

Section: DOSAGE AND ADMINISTRATION

FDA Comment: A separate section of the DOSAGE AND ADMINISTRATION should be drafted for the acne indication, and be specific for the regimen studied.

PRI Response: A separate DOSAGE AND ADMINISTRATION section specific to the acne indication has been drafted.

Also, an subheading has been added before the instructions for use of the product as an oral contraceptive. The proposed revisions of October 23rd to the oral contraceptive labeling to incorporate guidance for use of the product for acne have now been deleted. The attached DOSAGE AND ADMINISTRATION section for oral contraceptive use provides the approved language for that indication.

Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681 and specifically the draft labeling, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

NEW CORRESP
NC

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

OCT 31 1996

Ella Toombs, M.D.
Medical Reviewer
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Dr. Toombs:

In response to your request of October 31, 1996, please find enclosed a complete copy and a disk in WordPerfect 6.0 format of the current approved oral contraceptive labeling for ORTHO TRI-CYCLEN Tablets (norgestimate/ethinyl estradiol) revised to insert the changes of October 23 and 29, 1996 to the draft acne labeling. The draft of October 29th incorporated the requested revisions to the CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION sections of the Physicians' Package Insert. The original draft labeling for the additional acne indication was submitted on December 26, 1995 in New Drug Application 20-681.

Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681 and specifically the draft labeling, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

CENTER FOR DRUG REC'D NOV 01 1996 HFD EVALUATION AND RESEARCH

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THE R.W. JOHNSON
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NOV 11 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
Attn: DOCUMENT CONTROL ROOM N115
9201 Corporate Boulevard
Rockville, Maryland 20850

BC
NDA ORIG AMENDMENT

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

GENERALCORRESPONDENCE:
Environmental Assessment

Dear Sir/Madam:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) Tablets, which was submitted on December 26, 1995, for the additional indication for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy.

We would like to respond to FDA requests for additional information to complete their review of the environmental assessment documentation submitted on January 24, 1996. In responding, we have identified by date the specific request(s) from the Agency. This is followed by our response.

October 10, 1996

FDA request: We should provide certification or a statement that the drug substances norgestimate and ethinyl estradiol in ORTHO TRI-CYCLEN® Tablets meet the applicable environmental standards of the country in which they are manufactured.

PRI response: Please find enclosed as Attachment 1, statements from the manufacturers of the drug substances that their manufacturing operations are conducted in compliance with the applicable laws and regulations of that country. Norgestimate is supplied by and ethinyl estradiol is supplied by These documents were transmitted by facsimile to FDA on Oct. 30, 1996.

November 4, 1996

FDA request: 1. We should identify in the environmental assessment documents submitted on January 24, 1996, the information and documents

which are considered proprietary and therefore confidential, and that information which is non-confidential and suitable for public disclosure under the Freedom of Information Act.

2. We should provide Material Safety Data Sheets (MSDS) for each drug substance.

3. It was recommended that we determine whether we meet the criteria for Tier 0. If we qualify for Tier 0 status, then certain information would not be required in the Environmental Assessment (EA).

PRI response:

1. The entire contents of the January 24, 1996 submission to NDA 20-681 on environmental assessment should be considered PROPRIETARY and therefore the CONFIDENTIAL EA.

   Please find enclosed as Attachment 2 the NON-CONFIDENTIAL EA. The NON-CONFIDENTIAL EA is identical in content to the documents submitted on January 24, 1996, except certain numerical data in Items 6, 7 and 8 are now omitted because they are considered proprietary.

2. MSDSs are enclosed in Attachment 2 as an addendum to the NON-CONFIDENTIAL EA. These same documents are also enclosed in Attachment 3, as amendments to the CONFIDENTIAL EA.

3. Please find enclosed in Attachment 3 the information and calculations to support qualification for Tier 0 status. Despite qualification for Tier 0 status, we wish to affirm that the information in Items 7, 8, 9, 10 and 11 of the NON-CONFIDENTIAL EA is suitable for public disclosure.

We trust the above statements and enclosed information will faciliatate the FDA's review of environmental assessment information. Should you have any questions, please contact me at (908) 704-5108 or Heather Jordan at (908) 704-4607 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

cc: F. Cross (FDA) - desk copy

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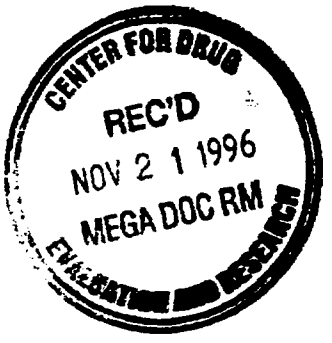

THE R.W. JOHNSON
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ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NOV 19 1996

Ella Toombs, M.D.
Medical Reviewer
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Dr. Toombs:

In response to your request of November 18, 1996, to revise the draft labeling for the acne indication submitted on October 31, 1996, to New Drug Application 20-681 for ORTHO TRI-CYCLEN® Tablets (norgestimate/ethinyl estradiol), please find the attached page from the draft labeling revised to address the two points discussed. Revisions have been made to Table II of the INDICATIONS AND USAGE section of the Physicians' Package Insert. A description of the changes are provided below.

Section: INDICATIONS AND USAGE

1. FDA Comment: FDA requested that we delete the "p" values from the table.

   PRI Response: The revision requested by the Agency has been made.

2. FDA Comment: FDA requested that the Physician's Global Assessment response be presented according to a hierarchy of response rather than grouping the subjects with a fair, good or excellent response under one heading.

   PRI Response: The revision requested by the Agency has been made. The percent of subjects with a fair, good or excellent response to ORTHO TRI-CYCLEN or Placebo has been added to Table II. The information is annotated to the Integrated Summary of Efficacy (ISE), Table 18, Vol. 1 of the original New Drug Application filed December 26, 1995. A copy of Table 18 from the ISE is also attached.

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Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681 and specifically the draft labeling, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

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ORIG AMENDMENT

EL

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

DEC 05 1996

Jonathan Wilkin, M.D.
Director
Center for Drug Evaluaton and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) for the acne indication. Reference is also made to revisions to the draft labeling recommended by the FDA which were provided by facsimile to the R.W. Johnson Pharmaceutical Research Institute on December 4, 1996. The revisions proposed by FDA affected two sections of the labeling, i.e., INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION. Prior agreement had been achieved with the Agency on all other sections of the labeling.

We would like to respond to the changes proposed by the FDA. The primary concern of the sponsor is with the language of the INDICATIONS AND USAGE statement. FDA's proposed text is provided below followed by the sponsor's proposed text and the supporting rationale.

FDA ORTHO TRI-CYCLEN is indicated 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.

Sponsor ORTHO TRI-CYCLEN is indicated for the treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy, desire contraception and have achieved menarche.

The sponsor agrees that the three primary considerations necessary for deciding whether to prescribe an oral contraceptive are addressed by this statement. They are that the patient: 1) has no known contraindications to oral contraceptive therapy, 2) has achieved menarche, and 3) desires contraception. The sponsor believes that the phrase

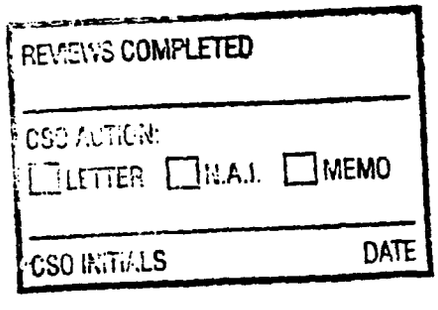
"unresponsive to topical anti-acne medications" is not necessary provided all three of the above criteria are met. This position is in agreement with that presented by the sponsor in the first meeting (November 10, 1992) with the Agency to discuss the proposed acne indication. In that initial meeting, the sponsor confirmed that the product would be indicated and marketed for those women needing treatment for facial acne who need or desire oral contraception. The sponsor's position on this point has not changed. Further, the patient type for whom an oral contraceptive would be prescribed for facial acne is one who meets the above criteria whether or not she has been responsive to topical anti-acne medication.

With regard to the age restriction proposed by the FDA, we believe that it is unnecessary provided the woman has achieved menarche. We recognize that the age stipulated by FDA corresponds to the lowest age of the women in the two acne studies. However, despite the ORTHO TRI-CYCLEN oral contraceptive clinical study protocols specifying an age restriction to women above 18 years of age, the Agency has not required the approved labeling for all oral contraceptive products to contain an age restriction provided the woman has achieved menarche and desires contraception. For this reason, we recommend the age restriction be deleted.

The FDA proposed additional changes to the paragraph and table presenting the combined results of the two clinical trials. The revisions proposed by the FDA are shown on the attached page with the heading "FDA Proposed Revisions of December 4, 1996". This page is followed by the proposed revision of the sponsor. This page has the heading "Sponsor Proposed Revisions of December 5, 1996". The changes proposed by the Agency deleted from the paragraph and the table, reference to the investigator's global assessment, one of the three primary efficacy variables. The sponsor believes that the investigator's global assessment should be retained in the text and table for the following reason. At the September 16, 1993 meeting with the Agency, there was extensive discussion of the primary efficacy variables. There was agreement that three primary efficacy measures would be evaluated: inflammatory lesion count, total lesion count and investigator's global assessment. It was further stated by the sponsor that all three efficacy parameters would need to be met to support efficacy. This was later confirmed with the agency in the pre-NDA meeting of September 25, 1995. Because of the agreement with the Agency that efficacy would be assessed by three criteria, we believe the investigator's global assessment should be added to the text and table. We agree with the Agency's proposal to delete mention of the secondary measures of efficacy from the paragraph.

The proposed revision to the DOSAGE AND ADMINISTRATION section is acceptable.

If it would facilitate the Agency's prompt resolution of the proposed labeling, the clinicians directing these studies would be available for a brief, very focused teleconference, should the Agency feel this would be helpful.



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DEC 05 1996

Should you have any questions or if I can be of further assistance in the Agency's review of NDA 20-681 and specifically the draft labeling, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann

Edward G. Brann
Assistant Director
Regulatory Affairs

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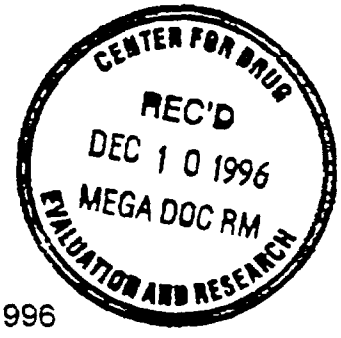

DELIVERED IN PERSON

December 10, 1996

Jonathan K. Wilkin, M.D.
Director
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, MD 20850

NDA 20-681
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Draft Labeling: Acne Indication

Dear Dr. Wilkin:

Reference is made to our pending New Drug Application 20-681 for ORTHO TRI-CYLEN for the acne indication. Reference is also made to the Agency's action letter of December 6, 1996 which states that the application is approvable pending submission of draft labeling for the product as recommended in the Agency's letter. The FDA recommended labeling had been provided to RWJPRI on December 4, 1996 and a response was submitted to the FDA on December 5, 1996.

After careful consideration of the Agency's action letter, we wish to adopt the FDA recommended labeling and, therefore, submit draft labeling which we certify is identical to that provided by the agency; as a result, this submission supersedes that of December 5, 1996. An electronic copy of the draft labeling is provided in WordPerfect 6.0 format. The redline shading in prior drafts has now been removed throughout the document.

This submission satisfies all requirements of the approvable letter in that it adopts the FDA recommended labeling as the claimed indication for this application. As no further review of information is required, we respectfully request the prompt issuance of an approval letter within the original PDUFA timeframe.

Should you have any questions or if I can be of further assistance in the Agency's review of this application, please contact me at (908) 704-5108 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

Edward G. Brann
Assistant Director
Regulatory Affairs

c: E. Toombs
K.D. White