CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-335

Name: Tri-Previfem™ Tablets
(Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg)

Sponsor: Andrx Pharmaceuticals, LLC

Approval Date: March 26, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

APPROVAL LETTER

ANDA 76-335

MAR 26 2004

Andrx Pharmaceuticals, LLC
Attention: William Stahovec
4955 Orange Drive
Ft. Lauderdale, FL 33314

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tri-Previfem Tablets (Norgestimate and Ethinyl Estradiol Tablets), 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg.

Reference is made to the Tentative Approval letter issued by this Office on January 6, 2004, and to your amendment dated January 9, 2004.

The listed drug product (RLD) referenced in your application, Ortho Tri-Cyclen of the RW Johnson Pharmaceutical Research Institute, was subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 4,530,839 (the '839 patent), 4,544,554 (the '554 patent), 4,616,006 (the '006 patent), and 4,628,051 (the '051 patent), expired on March 26, 2004. Your ANDA contains paragraph III patent certifications to each of the listed patents under Section 505(j)(2)(A)(vii)(III) of the Act. These certifications state that you will not market this drug product prior to the expiration of the patents.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Tri-Previfem Tablets (Norgestimate and Ethinyl Estradiol Tablets), 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, to be bioequivalent and therapeutically equivalent to the listed drug (Ortho Tri-Cyclen® Tablets,

0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, respectively, of RW Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/26/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-335
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-623/R.Trimmer/ 3-25-2004
HFD-623/D.Gill/ DSGill 3-25-04
HFD-617/C.Kiester/ 3/25/04
HFD-613/D.Catterson/ Debra M. Catterson 3/25/04
HFD-613/J.Grace/ RWW for 3/25/04

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F/T by: EW 3/25/04

APPROVAL

Robert West 3/26/2004

conc satisfactory
3/26/04.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

TENTATIVE APPROVAL LETTER

ANDA 76-335

JAN 6 2004

Andrx Pharmaceuticals, LLC
Attention: William Stahovec
2945 W. Corporate Lakes Blvd.
Weston, FL 33331

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, packaged in 28-day cycle regimens.

Reference is also made to your amendments dated July 17, 2002; and May 1, November 12, December 9, December 11, and December 30, 2003.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the patent/exclusivity issue noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Ortho Tri-Cyclen Tablets of Ortho McNeil Pharmaceutical, Inc., is currently subject to a period of patent protection. The following patents and their expiration dates are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

U.S. Patent No.	Expiration Date
4,530,839 ('839)	September 26, 2003
4,544,554 ('554)	September 26, 2003
4,461,006 ('006)	September 26, 2003
4,628,051 ('051)	September 26, 2003

Prior to September 26, 2003, the NDA holder, Ortho McNeil Pharmaceutical, Inc. (Ortho) submitted data in response to a written request letter from the agency for information concerning the use of the reference listed drug product, Ortho Tri-Cyclin Tablets, in a pediatric population. The filing of that submission by Ortho precluded the agency from granting final approval under 21 U.S.C. 355A(e) to your ANDA for up to 90 days while the agency determined whether the pediatric use data met the terms of the agency's written request. The agency completed its review and concluded that the pediatric data submitted by Ortho did meet the terms of the written request. As a result, on December 18, 2003, pediatric exclusivity was granted to Ortho's product, Ortho Tri-Cyclin (ethinyl estradiol; norgestimate) under NDA 19-697 and 20-690. This granting of pediatric exclusivity for Ortho Tri-Cyclin added a six-month period of marketing exclusivity to each of the patents listed above. Thus, the effective expiration date of these patents has been extended until March 26, 2004.

We note that your application contains a Paragraph III Certification to the '839, '554, '006 and '051 patents under Section 505(j)(2) (A)(vii)(III) of the Act. This certification states that Andrx Pharmaceuticals, LLC (Andrx) will not market its Norgestimate and Ethinyl Estradiol Tablets under this ANDA prior to the expiration of each of these patents. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '839, '554, '006 and '051 patents have expired, i.e., March 26, 2004.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made.

This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to March 26, 2004, you should amend your application accordingly.

Please be aware that we have requested the Division of Medication Errors and Technical Support (DMETS) to confirm the continued acceptability of your proposed proprietary name, Tri-Previfem Tablets, for this drug product. This is to provide assurance that the proposed name will be unlikely to cause confusion in the marketplace with other approved established and proprietary drug names. A satisfactory response from DMETS will be needed prior to final approval of this ANDA.

For further information on the status of this application or upon submitting an amendment to the application, please contact Sarah Park, Project Manager, at 301-827-5848.

Sincerely yours,

Gary Buehler 1/6/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-335
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-623/R.Trimmer/ 12-30-03
HFD-623/D.Gill/ for HFD-330 Decision
HFD-617/S.Park/ for 12/30/03
HFD-613/D.Catterson/ Debra M. Catterson 12/30/03
HFD-613/J. Grace/ 12/31/2003

Robert Lucet
1/6/2004

V:\FIRMSAM\ANDRX\LTRS&REV\76335.TA.doc
F/T by: gp/12/30/03

Faxed 1/6/04

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

APPROVED LABELING

TRI-PREVIFEM™
(norgestimate and ethinyl estradiol)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

TRI-PREVIFEM™
(norgestimate and ethinyl estradiol)

MAR 2 6 2004

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

TRI-PREVIFEM™
(norgestimate and ethinyl estradiol)

PRESCRIBING INFORMATION

℞ Only

DESCRIPTION

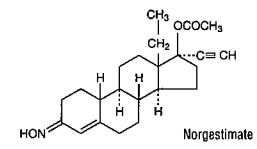
TRI-Previfem™ Tablets are a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

Each white tablet contains 0.18 mg of the progestational compound, norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, and pregelatinized starch.

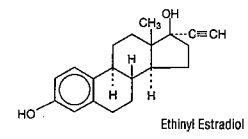
Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No.1 HT Aluminum Lake, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, and pregelatinized starch.

Each blue tablet contains 0.25 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No.1 HT Aluminum Lake, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, and pregelatinized starch.

Each teal tablet contains only inert ingredients, as follows: FD&C Blue No.2, Iron Oxide Yellow, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, and pregelatinized starch.



Norgestimate



Ethinyl Estradiol

CLINICAL PHARMACOLOGY

Oral Contraception

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93] Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Acne

Acne is a skin condition with a multifactorial etiology. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

Norgestimate and ethinyl estradiol are well absorbed following oral administration of norgestimate and ethinyl estradiol. On the average, peak serum concentrations of norgestimate and ethinyl estradiol are observed within two hours (0.5-2.0 hr for norgestimate and 0.75-3.0 hr for ethinyl estradiol) after administration followed by a rapid decline due to distribution and elimination. Although norgestimate serum concentrations following single or multiple dosing were generally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12 to 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6 to 14 hours.

Both norgestimate and ethinyl estradiol are extensively metabolized and eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged norgestimate was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of norgestimate have been identified in human urine following administration of radiolabeled norgestimate. These include 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5β-17-pregnan-20-yn,3α,17β-dihydroxy-13-ethyl,(17α), various hydroxylated metabolites and conjugates of these metabolites. Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

INDICATIONS AND USAGE

TRI-PREVIFEM™ Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

TRI-Previfem™ Tablets are 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.

Oral contraceptives are highly effective. **Table I** lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
	Typical Use[1] (2)	Perfect Use[2] (3)	(4)
Chance[4]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[6]		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Adapted from Hatcher et al., 1998 Ref. #1.

[1]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[2]Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[3]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

[4]The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[5]Foams, creams, gels, vaginal suppositories, and vaginal film.

[6]Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

[7]With spermicidal cream or jelly.

[8]Without spermicides.

In four clinical trials with norgestimate and ethinyl estradiol, the use-efficacy pregnancy rate ranged from 0.68 to 1.47 per 100 women-years. In total, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomized comparative clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2,312 patients on norgestimate and ethinyl estradiol, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 100 women-years.

In two double-blind, placebo-controlled, six month, multicenter clinical trials, norgestimate and ethinyl estradiol showed a statistically significant decrease in inflammatory lesion count and total lesion count (**Table II**). The adverse reaction profile of norgestimate and ethinyl estradiol from these two controlled clinical trials is consistent with what has been noted from previous studies involving norgestimate and ethinyl estradiol and are the known risks associated with oral contraceptives.

TABLE II: ACNE VULGARIS INDICATION
COMBINED RESULTS: TWO MULTICENTER, PLACEBO-CONTROLLED TRIALS
PRIMARY EFFICACY VARIABLES: EVALUABLE-FOR-EFFICACY POPULATION

	Norgestimate and Ethinyl Estradiol N = 163	Placebo N = 161
Mean Age at Enrollment	27.3 years	28.0
Inflammatory Lesions-Mean Percent Reduction	56.6	36.6
Total Lesions-Mean Percent Reduction	49.6	30.3

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems

a. Myocardial Infarction
An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN-YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE

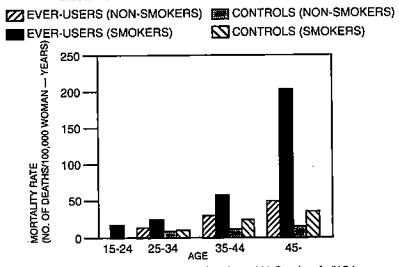


TABLE III. (Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see **CLINICAL PHARMACOLOGY**), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater [97].

b. Thromboembolism
An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast-feed or four weeks after a second trimester abortion.

c. Cerebrovascular Diseases
Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

d. Dose-Related Risk of Vascular Disease from Oral Contraceptives
A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of Risk of Vascular Disease
There are two studies, which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use
One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (**Table IV**). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

TABLE IV: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives Non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives Smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related
Adapted from H.W. Ory, ref. #35.

3. Carcinoma of the Reproductive Organs and Breasts
Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.[36-44,79-89]

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.[95]

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. Hepatic Neoplasia
Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. [50,51]

Studies have shown an increased risk of developing hepatocellular carcinoma [52-54,96] in oral contraceptive users. However, these cancers are rare in the U.S.

5. Ocular Lesions
There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral Contraceptive Use Before or During Early Pregnancy
Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. Gallbladder Disease
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. Carbohydrate and Lipid Metabolic Effects
Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS** 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with TRI-PREVIFEM™ Tablets there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed minimal, clinically insignificant changes from baseline to cycles 3, 12, and 24.

9. Elevated Blood Pressure
An increase in blood pressure has been reported in women taking oral contraceptives [68] and this increase is more likely in older oral contraceptive users [69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease [70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

10. Headache
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

11. Bleeding Irregularities
Breakthrough bleeding, and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

12. Ectopic Pregnancy
Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

1. Physical Examination and Follow Up
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding; appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Lipid Disorders
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. Liver Function
If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. Fluid Retention
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. Emotional Disorders
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. Contact Lenses
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. Drug Interactions
Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, and possibly with griseofulvin, ampicillin and tetracyclines.[72]

8. Interactions With Laboratory Tests
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.

e. High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. Carcinogenesis
See **WARNINGS** Section.

10. Pregnancy
Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** Sections.

11. Nursing Mothers
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. Pediatric Use
Safety and efficacy of norgestimate and ethinyl estradiol tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

13. Sexually Transmitted Diseases
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INFORMATION FOR THE PATIENT

See Patient Labeling printed below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (See **WARNINGS** Section).
- Thrombophlebitis and venous thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:
- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:
- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome

OVERDOSAGE
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS
The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]

Effects on menses:
- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Other effects:
- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

Oral Contraception
To achieve maximum contraceptive effectiveness, TRI-PREVIFEM™ Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. TRI-PREVIFEM™ Tablets are available in a blister pack tablet dispenser which is preset for a Sunday Start. Stickers designating a Day 1 Start are also provided.

28-Day Regimen (Sunday Start)
When taking TRI-PREVIFEM™ Tablets, the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take one active tablet daily for 21 days followed by one teal tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the **Detailed Patient Labeling** (**"How to Take the Pill"** section).

28-Day Regimen (Day 1 Start)
The dosage of TRI-PREVIFEM™ Tablets for the initial cycle of therapy is one active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1" followed by one teal tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the **Detailed Patient Labeling** (**"How to Take the Pill"** section).

The use of TRI-PREVIFEM™ for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See **CONTRAINDICATIONS** and **WARNINGS** concerning thromboembolic disease. See also **PRE-CAUTIONS** for **"Nursing Mothers."**) The possibility of ovulation and conception prior to initiation of medication should be considered.

(See **Discussion of Dose-Related Risk of Vascular Disease from Oral Contraceptives.**)

ADDITIONAL INSTRUCTIONS FOR ALL DOSING REGIMENS
Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

1. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive useshould be discontinued until pregnancy is ruled out.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

ACNE

The timing of initiation of dosing with norgestimate and ethinyl estradiol for acne should follow the guidelines for use of norgestimate and ethinyl estradiol as an oral contraceptive. **Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives.** The dosage regimen for norgestimate and ethinyl estradiol for treatment of facial acne, as available in a blister pack tablet dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one teal tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

HOW SUPPLIED

TRI-PREVIFEM™ Tablets are available in a blister pack tablet dispenser (NDC 62037-752-28) containing 28 tablets. Each white tablet contains 0.18 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each blue tablet contains 0.25 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each teal tablet contains inert ingredients.

The white tablets are round, unscored film coated, imprinted with the "△" on one side and "746" on the other side; The light blue tablets are round, unscored film coated, imprinted with the "△" on one side and "747" on the other side; the blue tablets are round, unscored film coated, imprinted with the "△" on one side and "748" on the other side; the teal tablets are round, film coated, imprinted with the "△" on one side and "743" on the other side.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

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BRIEF SUMMARY PATIENT PACKAGE INSERT

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy. TRI-PREVIFEM™ may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer ofthe breast or sex organs, jaundice or malignant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors.These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your health care provider.

TRI-PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. TRI-PREVIFEM™ is also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

TRI-PREVIFEM™ Tablets: Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each teal tablet contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your health care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:
Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterilization: <1%
Male sterilization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your health care provider if you have ever had any of these conditions. Your health care provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their health care provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or health care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk Of Developing Blood Clots

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast feeding or four weeks after a second trimester abortion. If you are breast feeding, you should wait until you have weaned your child before using the pill. (See also the section on **Breast Feeding** in **GENERAL PRECAUTIONS**.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart Attacks and Strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder Disease

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease although this risk may be related to pills containing high doses of estrogens.

4. Liver Tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the Reproductive Organs and Breasts

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases, which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives Non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives Smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related
Adapted from H.W. Ory, ref. #35.

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal Bleeding

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact Lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or health care provider.

3. Fluid Retention

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or health care provider.

4. Melasma

A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other Side Effects

Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or health care provider.

GENERAL PRECAUTIONS

1. Missed Periods and Use of Oral Contraceptives Before or During Early Pregnancy

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your health care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While Breast Feeding

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A

few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests
If you are scheduled for any laboratory tests, tell your doctor you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. Drug Interactions
Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually Transmitted Diseases
TRI-PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. TRI-PREVIFEM™ Tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.

Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.

On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or **IF YOU TAKE SOME MEDICINES,** including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE THAT IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" teal pills (without hormones).

There are 7 white "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

3. ALSO FIND:
1) where on the pack to start taking pills,

2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up method in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. TRI-PREVIFEM™ tablets are available in the blister pack tablet dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" white pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" white pill of the first pack during the first 24 hours of your period.
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white, light blue or blue "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.

2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** white or light blue "active" pills in a row in **Week 1 OR Week 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.

2. Then take 1 pill a day until you finish the pack.

3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD Week:**

1. If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:

THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white, light blue, or blue "active" pills in a row (during the first 3 weeks):

1. If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:

THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACK:

If you forget any of the 7 teal "reminder" pills in Week 4:

THROW AWAY the pills you missed.

Keep taking 1 pill each day until the pack is empty.

You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a **BACK-UP METHOD** anytime you have sex.

KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health care provider or pharmacist.

OTHER INFORMATION
Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits.

They are:
- menstrual cycles may become more regular
- blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- pain or other symptoms during menstruation may be encountered less frequently
- ectopic (tubal) pregnancy may occur less frequently
- noncancerous cysts or lumps in the breast may occur less frequently
- acute pelvic inflammatory disease may occur less frequently
- oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth control pills, ask your doctor/health care provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314

Rev. date: 03/03

7303

TRI-PREVIFEM™

(norgestimate and ethinyl estradiol)

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

TRI-PREVIFEM™ Tablets: Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each teal tablet contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your health care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:

Implant: <1%

Injection: <1%

IUD: 1 to 2%

Diaphragm with spermicides: 20%

Spermicides alone: 26%

Vaginal sponge: 20 to 40%

Female sterilization: <1%

Male sterilization: <1%

Cervical Cap with spermicides: 20 to 40%

Condom alone (male): 14%

Condom alone (female): 21%

Periodic abstinence: 25%

Withdrawal: 19%

No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your health care provider if you have ever had any of these conditions. Your health care provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their health care provider if they choose to use oral contraceptives.

Also, be sure to inform your doctor or health care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of Developing Blood Clots

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast feeding or four weeks after a second trimester abortion. If you are breast feeding, you should wait until you have weaned your child before using the pill. (See also the section on **Breast Feeding** in **GENERAL PRECAUTIONS**.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart Attacks and Strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder Disease

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease although this risk may be related to pills containing high doses of estrogens.

4. Liver Tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the Reproductive Organs and Breasts

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases, which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives Non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives Smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related
Adapted from H.W. Ory, ref. #35.

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal Bleeding

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact Lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or health care provider.

3. Fluid Retention

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or health care provider.

4. Melasma

A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other Side Effects

Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or health care provider.

GENERAL PRECAUTIONS

1. Missed Periods and Use of Oral Contraceptives Before or During Early Pregnancy

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your health care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. While Breast Feeding

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests

If you are scheduled for any laboratory tests, tell your doctor you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. Drug Interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an

See reverse side for additional information.

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DETAILED PATIENT LABELING (continued)

increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually Transmitted Diseases
TRI-PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. TRI-PREVIFEM™ Tablets is also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or **IF YOU TAKE SOME MEDICINES,** including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

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It is important to take it at about the same time every day.

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There are 7 white "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up method in case you miss pills.
AN EXTRA, FULL PILL PACK.

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You have a choice of which day to start taking your first pack of pills. TRI-PREVIFEM™ Tablets are available in the blister pack tablet dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" white pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" white pill of the first pack during the first 24 hours of your period.
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white, light blue or blue "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** white or light blue "active" pills in a row in **Week 1 OR Week 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. **You MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD Week**:

1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white, light blue, or blue "active" pills in a row (during the first 3 weeks):

1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a **BACK-UP METHOD** anytime you have sex.

KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE
The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health care provider or pharmacist.

OTHER INFORMATION
Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits.
They are:

- menstrual cycles may become more regular
- blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- pain or other symptoms during menstruation may be encountered less frequently
- ectopic (tubal) pregnancy may occur less frequently
- noncancerous cysts or lumps in the breast may occur less frequently
- acute pelvic inflammatory disease may occur less frequently
- oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth control pills, ask your doctor/health care provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314

Rev. date: 03/03

TRI-PREVIFEM™

(norgestimate and ethinyl estradiol)

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

TRI-PREVIFEM™ Tablets: Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each teal tablet contains inert ingredients.

BRIEF SUMMARY PATIENT PACKAGE INSERT

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy. TRI-PREVIFEM™ may also be taken to treat moderate acne in females who are able to use the pill. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the **Detailed Patient Labeling**. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility pills may cause such cancers.

Taking the combination pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The **Detailed Patient Labeling** information gives you further information which you should read and discuss with your health care provider.

TRI-PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. TRI-PREVIFEM™ Tablets is also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL
IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or **IF YOU TAKE SOME MEDICINES,** including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE THAT IT HAS 28 PILLS:
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" teal pills (without hormones).
There are 7 white "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up method in case you miss pills.

AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. TRI-PREVIFEM™ Tablets are available in the blister pack tablet dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" white pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" white pill of the first pack during the first 24 hours of your period.
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white, light blue or blue "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** white or light blue "active" pills in a row in **Week 1 OR Week 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

See reverse side for additional information.

BRIEF SUMMARY PATIENT PACKAGE INSERT (continued)

If you **MISS 2** blue "active" pills in a row in **THE 3RD Week:**

1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white, light blue, or blue "active" pills in a row (during the first 3 weeks):

1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, **THROW OUT** the rest of the pack and start a new pack of pills that same day.

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.

3. You **MAY BECOME PREGNANT** if you have sex in the 7 days after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 teal "reminder" pills in **Week 4**:

THROW AWAY the pills you missed.

Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a **BACK-UP METHOD** anytime you have sex.

KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

INSTRUCTIONS FOR USING YOUR BLISTER PACK DISPENSER

PLEASE READ ME!

✎
☐ Sunday Start
Or
☐ Day 1 Start

There are two ways to start taking birth control pills, Sunday Start or Day 1 Start. Your health care provider will tell you which to use.

Save these instructions.

1
If this is the first time you are taking birth control pills, or if you have not taken birth control pills for 10 days or more, your first step is to **wait until the first day you get your menstrual period.** Then, follow these instructions for either Sunday Start or Day 1 Start.

2
☐ Sunday Start
☐ Day 1 Start

When you get your period:
- You will use a **Sunday Start** if your doctor told you to take your first pill on a Sunday. Take pill "1" on the Sunday after your period starts. If your period starts on a Sunday, take pill "1" that day.
- You will use a **Day 1 Start** if your doctor told you to take pill "1" on the first day of your period.

3
Sunday Start: Place label, which starts on a Sunday (SUN) on top row of pills.

Day 1 Start: Place label, which corresponds to the first day of your period (if your period starts on Tuesday (TUE), start the labels with TUE beginning first.

4
Remove pill "1" by pushing down on the pill. The pill will come out through the foil in the back.

5
Swallow the pill. You will take one pill each day, if you use a Sunday Start and you are taking the pill for the **FIRST TIME, YOU MUST USE A BACK-UP METHOD OF BIRTH CONTROL FOR THE FIRST 7 DAYS.** If you use a Day 1 Start, you are protected from becoming pregnant as soon as you take your first pill.

6
Wait 24 hours to take your next pill. To take pill "2", proceed to next pill in blister pack. Continue to take one pill each day until all the pills have been taken.

7
Take your pill at the same time every day. It is important to take the correct pill each day and not miss any pills. To help you remember, take your pill at the same time as another daily activity, like turning off your alarm clock or brushing your teeth.

8
When your refill is empty,
- You will start a new refill on the day after pill "28".

9
THE FIRST PILL IN EVERY REFILL WILL ALWAYS BE TAKEN ON THE SAME DAY OF THE WEEK, NO MATTER WHEN YOUR NEXT PERIOD STARTS.

If you miss one pill... take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day. You will not need a back-up method of birth control if you have sex.

If you miss two or more pills in a row... YOU MAY BECOME PREGNANT, if you have sex during the next 7 days!

YOU MUST USE A BACK-UP METHOD OF BIRTH CONTROL, (condoms, foam, or sponge) for those 7 days and follow the instructions below.

LOOK AT THE PILL NUMBERS ON YOUR REFILL – the instructions below depend on which pills you miss, and if you used a Sunday Start or Day 1 Start.

☐ **Sunday Start** ✎
a. If you miss two pills in a row of pills 1 through 14:
Take two pills as soon as you remember and two pills the next day, then keep taking one pill each day as usual.

b. If you miss pills **14 and 15** or
if you miss two pills in a row of pills **15 through 21** or
if you miss three or more pills in a row of pills **1 through 21:**
Keep taking one pill each day until Sunday.
*On Sunday, **THROW OUT** the rest of the pills and start a new refill.*

☐ **Day 1 Start** ✎
a. If you miss two pills in a row of pills **1 through 14:**
Take two pills as soon as you remember and two pills the next day, then keep taking one pill each day as usual.

b. If you miss pills **14 and 15** or
if you miss two pills in a row of pills 15 through 21 or
if you miss three or more pills in a row of pills **1 through 21:**
***THROW OUT** the rest of the pills and start a new refill that day.*

If you miss pills 22 through 28...
Remember that pills 22 through 28 are "reminder" pills and do not contain active ingredients.
- If you miss any of pills 22 through 28, you will still be protected:
Throw away the missed pills and keep taking one pill each day until you finish the refill. Start a new refill on the day after pill "28".

Side Effects:
Some side effects are normal and will go away after the first 1, 2 or 3 months as your body gets used to the pill. For more information on side effects see the Brief Summary, the Detailed Patient Information Labeling that comes with your pills, or ask your health care provider or pharmacist.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314

Rev. date: 03/03 7302

ANDA #76-335

TRI-PREVIFEM™

(norgestimate and ethinyl estradiol)

FINAL PRINTED LABELING

HOW TO USE THIS BLISTER PACK

MON	TUE	WED	THU	FRI	SAT	SUN
TUE	WED	THU	FRI	SAT	SUN	MON
WED	THU	FRI	SAT	SUN	MON	TUE
THU	FRI	SAT	SUN	MON	TUE	WED
FRI	SAT	SUN	MON	TUE	WED	THU
SAT	SUN	MON	TUE	WED	THU	FRI

APPROVED MAR 6 2004

FOR USE WITH DAY 1 START REGIMEN ONLY

NOTICE

Oral contraceptives are intended to prevent pregnancy. They do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases.

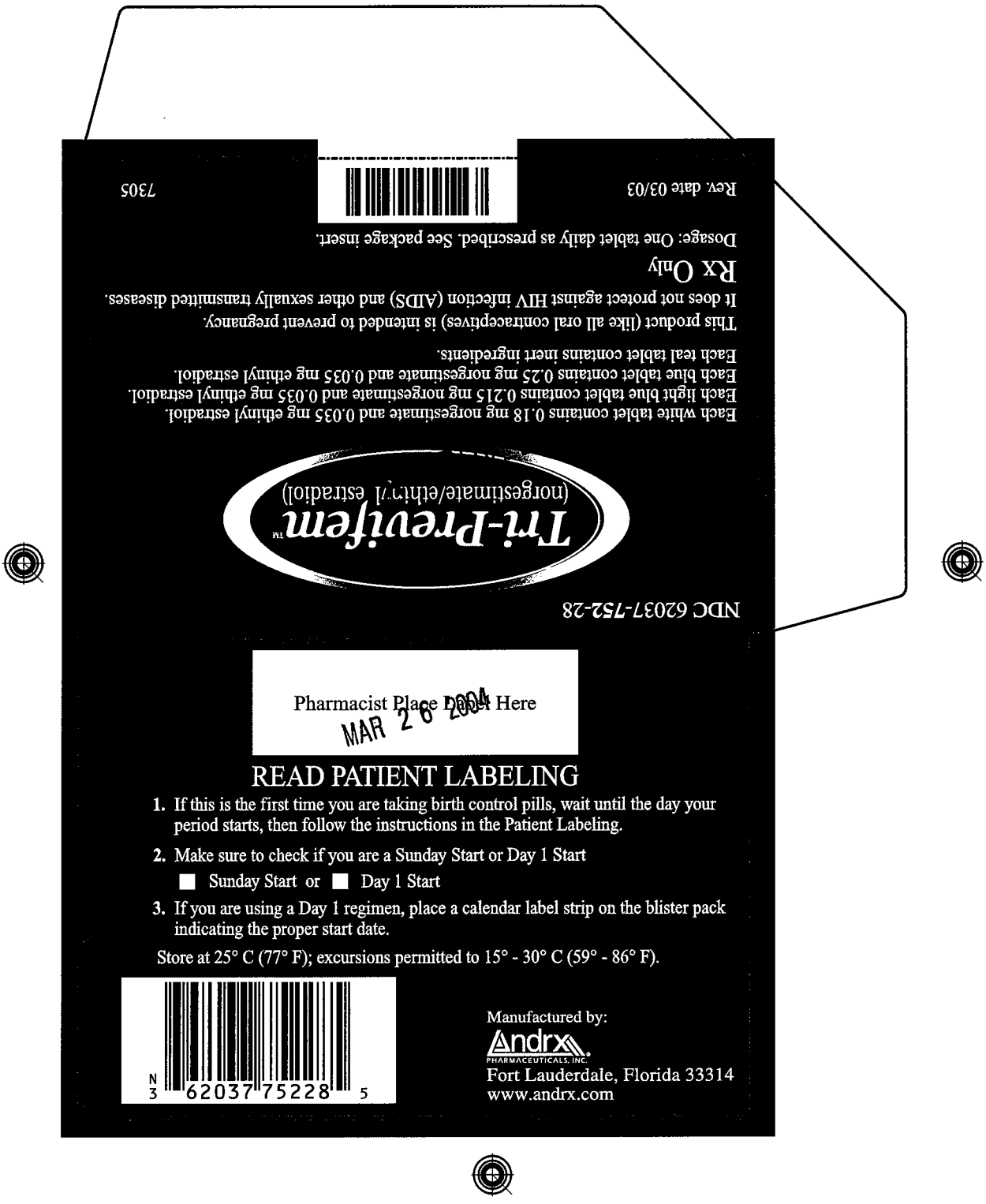
USE OF CALENDER LABEL (On the other side)

- **If Sunday start, discard calendar label.**
- **If DAY 1 START:**
  1. **Find the label strip (see other side) that starts with the day of the week your period begins.**
  2. **Peel that label strip and place it on the top of the blister pack across the area where each day of the week is printed.**
  3. **Firmly press label on blister pack.**

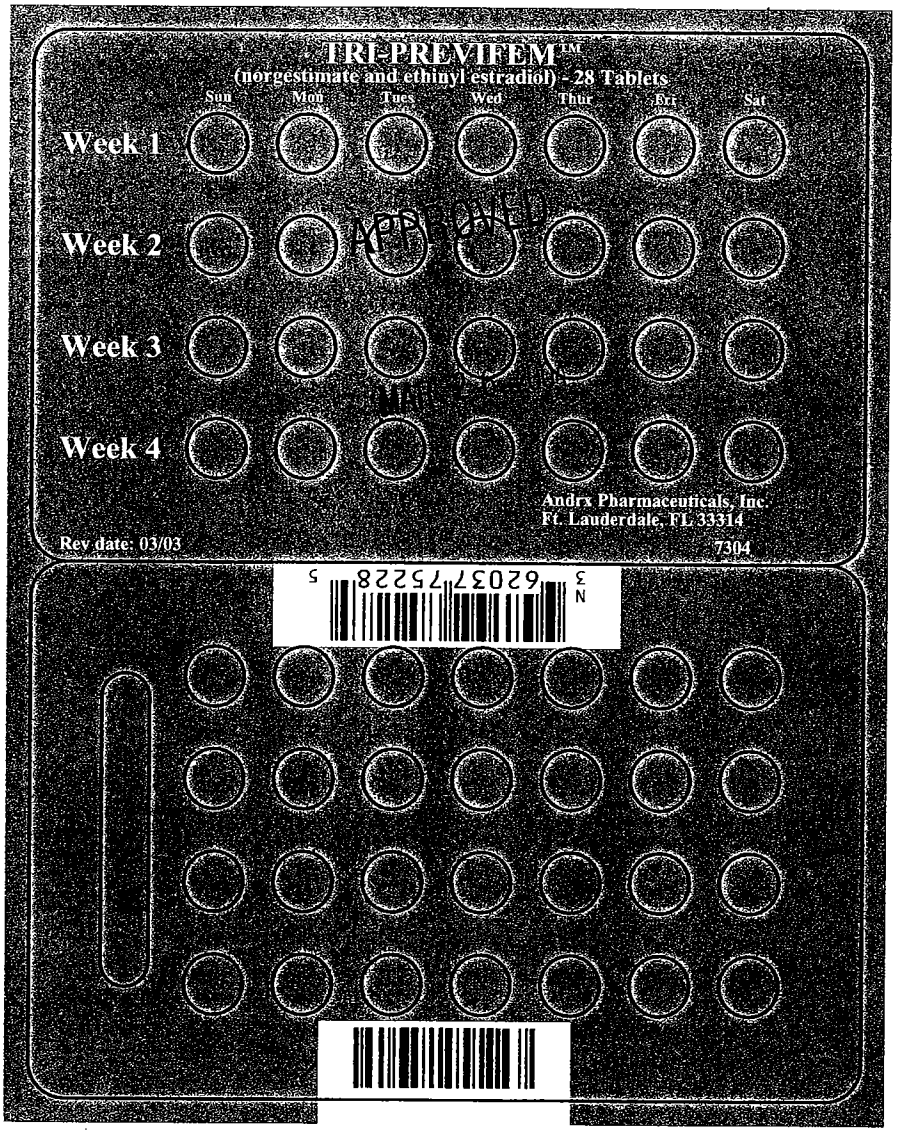
Rev date: 03/03

7306

ANDA #76-335
TRI-PREVIFEM™
(norgestimate and ethinyl estradiol)
FINAL PRINTED LABELING



ANDA #76-335
TRI-PREVIFEM™
(norgestimate and ethinyl estradiol)
FINAL PRINTED LABELING



NDC 62037-752-28

Tri-Previfem™
(norgestimate/ethinyl estradiol)

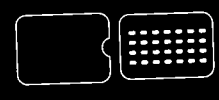
Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol.
Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol.
Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol.
Each teal tablet contains inert ingredients.

Rx Only

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F).

6 Blister Packs 28 Day Regimen

Contains: 6 Blister Packs,
28 Tablets Each and
6 Label Strips



Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida 33314
www.andrx.com

7307

6 Blister Packs 28 Day Regimen

Tri-Previfem™
(norgestimate/ethinyl estradiol)

Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol.
Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol.
Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol.
Each teal tablet contains inert ingredients.

Dosage: One tablet daily as prescribed. See package insert.

Important: Each pouch contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.

Rx Only
Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida 33314
www.andrx.com

N3 62037 75228 5

Tri-Previfem™
(norgestimate/ethinyl estradiol)

Contains: 6 Blister Packs,
28 Tablets Each and
6 Label Strips

6 Blister Packs 28 Day Regimen

NDC 62037-752-28

Tri-Previfem™
(norgestimate/ethinyl estradiol)

Contains: 6 Blister Packs,
28 Tablets Each and
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Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol.
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Rx Only

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F).

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida 33314
www.andrx.com
Rev. date 03/03 7307

6 Blister Packs 28 Day Regimen

Tri-Previfem™
(norgestimate/ethinyl estradiol)

Each white tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol.
Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol.
Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol.
Each teal tablet contains inert ingredients.

Contains: 6 Blister Packs, 28 Tablets Each and 6 Label Strips

Rx Only

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida 33314
www.andrx.com

Lot:
Exp:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-335

Date of Submission: December 27, 2001 (Original) and July 17, 2002 (Amendment)

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg (28 day regimen)

Proprietary Name: Tri-Previfem™ Tablets

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   We have completed our nomenclature review and have no objection to the use of the proprietary name "Tri-Previfem™" for your drug product.

2. **CONTAINER** (Blister Pack Tablet Dispenser – 28 Day):
3. **CALENDAR LABEL STRIP** (To be affixed to the blister pack):
4. **CARDBOARD SLEEVE** (To contain the blister pack and calendar label strip):
5. **CARTON** (Box of 6 blister packs):

   Please refer to pages "0036-40" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions.

6. **PROFESSIONAL PACKAGE INSERT**:

   Please refer to pages "0043-48, 0050-51, 0053, 0056-57, 0059, 0061-64, 0069, 0071-72, 0076, 0079-81, and 0083" of the attached mocked-up copy of your draft insert labeling for all of the requested labeling revisions:

7. **BRIEF SUMMARY PATIENT PACKAGE INSERT**:

   Please refer to pages "0087, 0089, and 0093-96" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions:

8. **DETAILED PATIENT LABELING INSERT**:

   Please refer to page "0071-72, 0076, 0079-81, and 0083" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions:

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Mocked-up copy of the firm's draft labeling.

APPEARS THIS WAY
ON ORIGINAL

35 pages of draft labeling have been removed from this portion of the document.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Tri-Previfem™" was found acceptable by DMETS on October 8, 2002 (Consult #02-0160)**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	III	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	III	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 0006-7.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Ft. Lauderdale, FL 33314 [Vol. A1.2 pg. 0390.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted] on bright side and [redacted] on matte side.
[Vol. A1.3 pg. 0859-870.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling is NOT accurate according to the composition statement. I have asked the firm to revise. [Vol. A1.1 pg. 0275-76.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Blister Pack Tablet Dispenser with cardboard sleeve.

[Vol. A1.3 pg. 0871.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: None. (However I have asked the firm to include their storage temp. statement on their labeling.)
[Vol. A1.1 pg. 0162.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **IMPORTANT:** Each carton contains Detailed Patient Labeling and each DIALPAK® Tablet Dispenser contains the Brief Patient Labeling. Both should be included with each package dispensed to the patient.
ANDA: **IMPORTANT:** Each sleeve contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
[Vol. A1.1 pg. 0122.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.18 mg/0.035 mg tablet:	"white, round, film coated, tablet with Andrx logo on one side and **746** on the other side."
0.215 mg/0.035 mg tablet:	"light blue, round, film coated, tablet with Andrx logo on one side and **747** on the other side."
0.25 mg/0.035 mg tablet:	"blue, round, film coated, tablet with Andrx logo on one side and **748** on the other side."
placebo tablet:	"teal, round, film coated, tablet with Andrx logo on one side and **743** on the other side."

I have asked the firm to include "unscored" in the description of the active tablets.
[Vol. A1.3 pg. 0897 and 0911.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on January 28, 2003, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Tri-Previfem™" for their product. DMETS concluded on October 8, 2002, that "Tri-Previfem" was an acceptable name for this drug product (Consult #02-0160).

Date of Review: 3/4/03 Dates of Submission: 12/27/01 and 7/17/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 3/5/03

Team Leader: John Grace Date:

John D Grace 3/5/2003

cc:

ANDA: 76-335
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\andrx\ltrs&rev\76335NA1.L.doc
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-335

Date of Submission: May 1, 2003 (Amendment – FPL)

Applicant's Name: Andrx Pharmaceuticals, L.L.C.

Established Name: Norgestimate and Ethinyl Estradiol Tablets (Triphasic Regimen) (28 day regimen)

Proprietary Name: Tri-Previfem™ Tablets

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels (Blister Pack Tablet Dispenser – 28 Day):
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

CALENDAR LABEL STRIP (To be affixed to the blister pack):
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

CARDBOARD SLEEVE (To contain the blister pack and calendar label strip):
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

CARTON (Box of 6 blister packs):
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT:
Satisfactory as of the May 1, 2003 submission. [Vol. 3.1, Rev. date: 03/03]

Revisions needed post-approval: **Yes**. There were several labeling revisions that were editorial in nature, and therefore could be "post-approval" revisions. I communicated these post-approval revisions to Jamie Rance, of Andrx Pharmaceuticals, L.L.C., by telephone and by facsimile.

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	III	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	III	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ORTHO-TRI-CYCLEN® Tablets

NDA Number: 19-697

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-697/S-022: Approved June 5, 2000; and S-024 (Combination Detailed Patient and Brief Summary Insert only): Approved January 16, 2001

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	x		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? **The proposed name "Tri-Previfem™" was found acceptable by DMETS on October 8, 2002 (Consult #02-0160). On June 6, 2003, I asked DMETS to perform a final review on the proprietary name, and on July 1, 2003, DMETS gave the final OK (Consult #02-0160-1). However, "Tri-Previfem" will need another re-review from DMETS, since it has been over 90 days since the final OK was given.**	x		

PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-697

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4530839	Sept. 26, 2003	U-112	Contraception	III	None
4544554	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4616006	Sept. 26, 2003	U-66	Triphasic Regimen	III	None
4628051	Sept. 26, 2003	U-66	Triphasic Regimen	III	None

Exclusivity Data– NDA 19-697

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 0006-7.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Ft. Lauderdale, FL 33314 [Vol. A1.2 pg. 0390.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted] on bright side and [redacted] on matte side.

[Vol. A1.3 pg. 0859-870.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the components and composition statement. [Vol. A1.1 pg. 0275-76.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Blister Pack Tablet Dispenser with cardboard sleeve.
[Vol. A1.3 pg. 0871.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F).
I have asked the firm to include the statement "[see USP Controlled Room Temperature]" as a post-approval revision.

[Vol. A1.1 pg. 0162.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **IMPORTANT:** Each carton contains Detailed Patient Labeling and each DIALPAK® Tablet Dispenser contains the Brief Patient Labeling. Both should be included with each package dispensed to the patient.
ANDA:**IMPORTANT:** Each sleeve contains a combination Brief Summary Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.
[Vol. A1.1 pg. 0122.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

0.18 mg/0.035 mg tablet: "white, round, unscored, film coated, tablet with Andrx logo on one side and **746** on the other side."
0.215 mg/0.035 mg tablet: "light blue, round, unscored, film coated, tablet with Andrx logo on one side and **747** on the other side."
0.25 mg/0.035 mg tablet: "blue, round, unscored, film coated, tablet with Andrx logo on one side and **748** on the other side."

placebo tablet: "teal, round, film coated, tablet with Andrx logo on one side and **743** on the other side."

[Vol. A1.3 pg. 0897 and 0911.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on January 28, 2003, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Tri-Previfem™" for their product. DMETS concluded on October 8, 2002, that "Tri-Previfem" was an acceptable name for this drug product (Consult #02-0160). On June 6, 2003, I asked DMETS to perform a final review on the proprietary name, and on July 1, 2003, DMETS gave the final OK (Consult #02-0160-1). However, "Tri-Previfem" will need another re-review from DMETS, since it has been over 90 days since the final OK was given.

Date of Review: 10/30/03 Date of Submission: 5/01/03

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 10/31/03

Team Leader: John Grace Date:

10/31/2003

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cc:

ANDA: 76-335
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\andrx\ltrs&rev\76335APL.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

CHEMISTRY REVIEW(S)

ANDA #76-335

Norgestimate and Ethinyl Estradiol Tablets
0.250 mg/0.035 mg
0.215 mg/0.035 mg
0.180 mg/0.035 mg

Andrx Pharmaceuticals, Inc.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA #**76-335**

2. REVIEW #: **01**

3. REVIEW DATE: May 8, 2002

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	n/a

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
76-335	27. Dec. 2001

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, Inc.*

Address: 4955 Orange Drive
Fort Lauterdale, FL 33314

Representative: Diane Servello, Sr. Director of Reg. Affairs

Telephone: 954-585-1846; fax 954-584-1422

Chemistry Review Data Sheet

. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: n/a
b) Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ; Oral-28 Day Regimen – NDA 19697) manufactured by Johnson RW.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-335: Norgestimate and Ethinyl Estradiol Tablets: **0.180 mg/0.035 mg and 0.215 mg/0.035 and 0.250 mg/0.035 mg (28 day).**

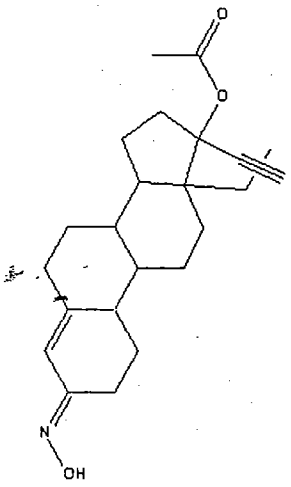
13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
x Not a SPOTS product

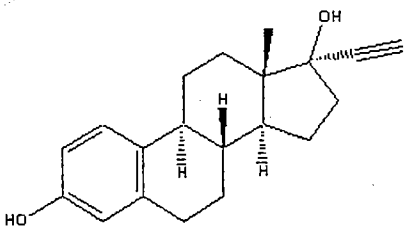
. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

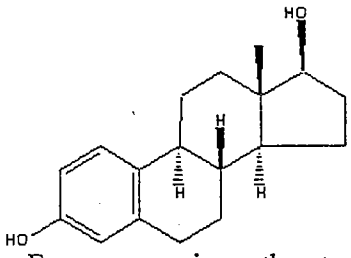
Norgestimate; [35189-28-7], $C_{23}H_{31}NO_3$ MW 369.5028



APPEARS THIS WAY
ON ORIGINAL

Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084





For a comparison: the structure of the related Estradiol molecule.

[redacted] an impurity

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	adequate	12-27-2000	
	II			1	not adequate	05-24-2002	12 deficiencies
	III			4	n/a		
	III			4	n/a		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Norgestimate and Ethinyl Estradiol Tablets	76-334	0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets	76-335	0.180 mg/0.035 mg and 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg / 0.035 mg ——— 28 day regimens)	75-804 [1st generic]	**0.250 mg/0.035 mg**
Norgestimate and Ethinyl Estradiol Tablets	75-808	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	district goal date =	Nov. 2002	
Methods Validation	open		
Labeling	open		D.Catterson
Bioequivalence	open		
Environ. Ass.	sat		
Radiopharmaceutical	n/a		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes If no, explain reason below:

The Chemistry Review for ANDA 76-335

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval at this time.

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

n/a

II. Summary of Chemistry Assessments

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

Drug Product:

Norgestimate and Ethinyl Estradiol Tablets **0.250 mg/0.035 mg**

The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW. Andrx will market this drug product only in blisters at this time.

Drug Substances:

Norgestimate:

This is not a USP drug substance but is described in the FP (vol. 36 [September – October 2000]). It is a steroid which possesses antifertility and pregestatioal activity. It exists as an equilibrium mix of syn and anti isomers.

Ethinyl Estradiol:

A USP drug substance, a crystalline powder with a MW of 296.41 The firm uses the USP analytical method to monitor assay and their own method for monitoring impurities.

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

The labeling should describe its use.

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Robert W. Trimmer, Ph.D./
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./ 7-15-02
ProjectManagerName/Date:	Ruby Wu, PM/ 7/16/02 for

C. CC Block

ANDA 76-334/76-335
ANDA dup
DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

5. Please provide a commitment to file the following information via a CBE-0 post-approval supplement when using the alternate manufacturing site for the drug substance: (a) comparative dissolution between the ANDA batch and the first batch of the drug product using the drug substance from the alternate site, (b) the first commercial batch of drug product, with a COA, using the drug substance from the alternate site on the long-term stability program, and (c) stability data table to indicated the drug substance site of manufacture.

Sincerely yours,

Paul Schwartz for 7/23/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Redacted 48 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 76-335
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. /7/9/02 7-19-2002

HFD-623/ Upinder Atwal for Dave S. Gill, Ph.D. /7/18/02 7/29/02 for

HFD-617/S. Kim,Pharm. D. /7/19/02 7/22/02

F/T by gp/7/19/02

V:\FIRMSAM\ANDRX\LTRS&REV\76335.cr1.Norgestimate-EE.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

c: **76334cr1.Norgestimate-EE.doc**

APPEARS THIS WAY
ON ORIGINAL

ANDA #76-335

Norgestimate and Ethinyl Estradiol Tablets
0.250 mg/0.035 mg
0.215 mg/0.035 mg
0.180 mg/0.035 mg
(28-day regimen)

Andrx Pharmaceuticals, L.L.C.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA # **76-335**

2. REVIEW #: **02**

3. REVIEW DATE: May 31, 2003

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
original	12-~~11~~-2001 (27)
Bio amendment	12-12-2002
NC re change in ownership	01-06-2003
FDA	FDA
Bio review	01-28-2003 acceptable
NA letter	07-23-2002

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
76-335	11-22-2002 amendment

3-25-03 RS 7-3-03

Chemistry Review Data Sheet

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, L.L.C.*

Address: 4955 Orange Drive
Fort Lauterdale, FL 33314

Representative: William Stahovec

Telephone: 954-358-6124 fax 954-358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: *n/a*
b) Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ; Oral-28 Day Regimen – NDA 19697) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-335: Norgestimate and Ethinyl Estradiol Tablets: **0.180 mg/0.035 mg and 0.215 mg/0.035 and 0.250 mg/0.035 mg (28 day).**

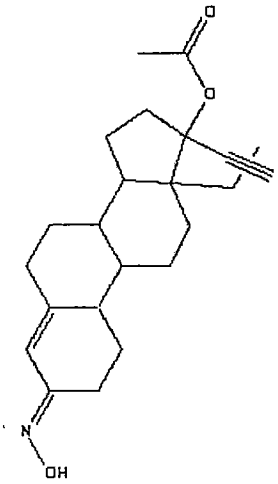
13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

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

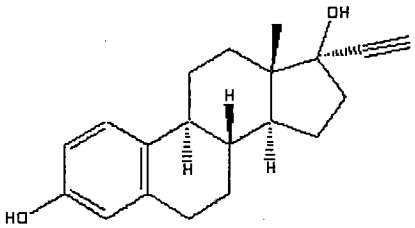
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

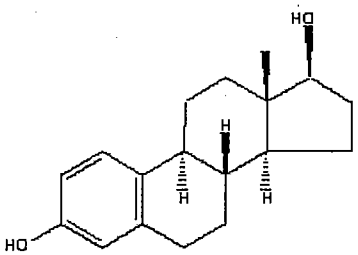
Norgestimate; [35189-28-7], $C_{23}H_{31}NO_3$ MW 369.5028



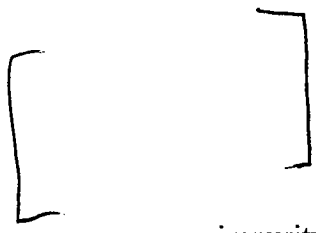
APPEARS THIS WAY
ON ORIGINAL

Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084





For a comparison: the structure of the related Estradiol molecule.



an impurity

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	**DATE REVIEW COMPLETED**	COMMENTS
	II			3	adequate	5-1-2002 Dr.Raw	NC to 5-23-03
	II			1	adequate	04-03-2003	
	III			4	n/a		
	III			4	n/a		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Norgestimate and Ethinyl Estradiol Tablets	76-334	0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets	76-335	0.180 mg/0.035 mg and 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg / 0.035 mg ——28 day regimens)	75-804 [1st generic]	**0.250 mg/0.035 mg**
Norgestimate and Ethinyl Estradiol Tablets	75-808	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	*n/a*		
EES	adequate	04-30-2003	
Methods Validation	DP not USP – open		
Labeling	Pending	01-28-2003	N. Tran
Bioequivalence	adequate		
Environ. Ass.	sat. CR1		
Radiopharmaceutical	*n/a*		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes If no, explain reason below:

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confidential commercial

information from

CHEMISTRY REVIEW #2 (pp. 8-18)

The Chemistry Review for ANDA 76-335

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval at this time.

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

n/a

II. Summary of Chemistry Assessments

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

Drug Product:

Norgestimate and Ethinyl Estradiol Tablets **0.250 mg/0.035 mg**

The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW. Andrx will market this drug product only in blisters at this time.

Drug Substances:

Norgestimate:

This is now a USP drug substance. It is a steroid which possesses antifertility and pregestatioal activity. It exists as an equilibrium mix of syn and anti isomers.

Ethinyl Estradiol:

A USP drug substance, a crystalline powder with a MW of 296.41 The firm uses the USP analytical method to monitor assay and their own method for monitoring impurities.

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

The labeling should describe its use.

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted regarding [redacted] issues, [redacted] of tablets issue.

III. Administrative

A. Reviewer's Signature

6-16-03

B. Endorsement Block

ChemistName/Date:	Robert W. Trimmer, Ph.D./
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./
ProjectManagerName/Date:	Sarah Kim, PM/

C. CC Block

ANDA 76-335
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ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #2

e. Please provide 3 months of accelerated stability data that support the 20 minute dissolution time (recommended by our Division of Bioequivalence).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

2. Please provide updated stability data for all strengths for the drug product.

Sincerely yours,

Paul S. Seo for 6/30/03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: **ANDA 76-335**
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. 6-16-03

HFD-623/ Dave S. Gill, Ph.D. 6-16-03

HFD-617/S. Kim, Pharm. D. for 6/16/03

F/T by /ard/6/11/03

V:\FIRMSAM\ANDRX\LTRS&REV\76335.cr2.Norgestimate-EE.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

c: **76334cr2.Norgestimate-EE.doc**

APPEARS THIS WAY
ON ORIGINAL

ANDA #76-335

Norgestimate and Ethinyl Estradiol Tablets
0.250 mg/0.035 mg
0.215 mg/0.035 mg
0.180 mg/0.035 mg
(28-day regimen)

Andrx Pharmaceuticals, L.L.C.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA # **76-335**

2. REVIEW #: **03**

3. REVIEW DATE: September 24, 2003

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-27-2001
Amendment	11-22-2002
Bio amendment	12-12-2002
NC re change in ownership	01-06-2003
Gratuitous Amendment	03-25-2003
amendment	08-11-2003
FDA	FDA
Bio review	01-28-2003 acceptable
NA letter	07-23-2002

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	08-11-2003

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, L.L.C.*

Address: 2945 West Corporate Lakes Blvd.
Weston, FL 33331

Representative: William Stahovec

Telephone: 954-358-6124 fax 954-358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: *n/a*
b) Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS for SUBMISSION:
The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ; Oral-28 Day Regimen – NDA 19697) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-335: Norgestimate and Ethinyl Estradiol Tablets: **0.180 mg/0.035 mg and 0.215 mg/0.035 and 0.250 mg/0.035 mg (28 day).**

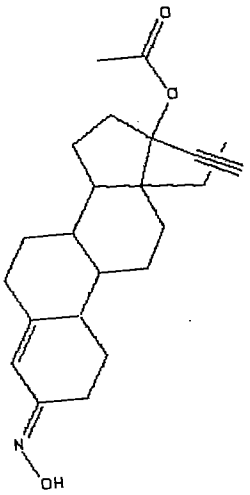
13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__x__ Not a SPOTS product

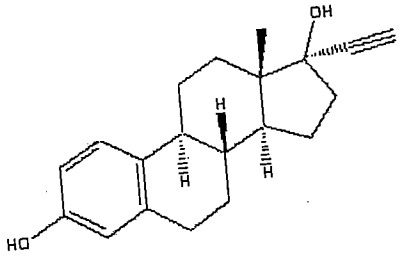
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

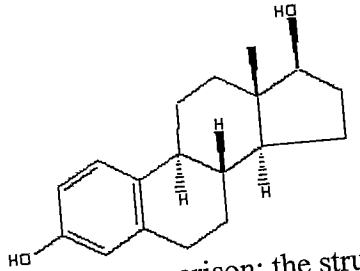
Norgestimate; [35189-28-7], $C_{23}H_{31}NO_3$ MW 369.5028



APPEARS THIS WAY
ON ORIGINAL

Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084





For a comparison: the structure of the related Estradiol molecule.

[redacted] an impurity

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	adequate	5-1-2002 Dr.Raw	NC to 5-23-03
	II			1	adequate	04-03-2003	
	III			4	n/a		
	III			4	n/a		

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

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

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Norgestimate and Ethinyl Estradiol Tablets	76-334	0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets	76-335	0.180 mg/0.035 mg and 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg / 0.035 mg ——— 28 day regimens)	75-804 [1st generic]	**0.250 mg/0.035 mg**
Norgestimate and Ethinyl Estradiol Tablets	75-808	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	*n/a*		
EES	adequate	04-30-2003	
Methods Validation	DP not USP – open		
Labeling	Pending		D. Caterson
Bioequivalence	adequate	01-28-2003	N. Tran
Environ. Ass.	sat. CR1		
Radiopharmaceutical	*n/a*		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes If no, explain reason below:

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information from

CHEMISTRY REVIEW #3 (PP. 8-14)

The Chemistry Review for ANDA 76-335

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval at this time.

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

n/a

II. Summary of Chemistry Assessments

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

Drug Product:

Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg

The listed reference drug product is **Ortho-Tri Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19697) manufactured by Johnson RW. Andrx will market this drug product only in blisters at this time.

Drug Substances:

Norgestimate:

This is now a USP drug substance. It is a steroid which possesses antifertility and pregestatioal activity. It exists as an equilibrium mix of syn and anti isomers.

Ethinyl Estradiol:

A USP drug substance, a crystalline powder with a MW of 296.41 The firm uses the USP analytical method to monitor assay and their own method for monitoring impurities.

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

The labeling should describe its use.

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted regarding ——— issues, missing data, and the dissolution specification.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Robert W. Trimmer, Ph.D./9/30/03 10-10-03
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./
ProjectManagerName/Date:	Sarah Kim, PM/

C. CC Block

ANDA 76-335
ANDA dup
DIV FILE
Field Copy

Redacted 35 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: **ANDA 76-335**
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. /9/30/03 10-10-03
HFD-623/ Dave S. Gill, Ph.D. /10/2/03 DS Gill 10-15-03
HFD-617/S. Kim, Pharm. D. /10/9/03 S. Kim 10/15/03

F/T by / ard/10/10/03

C:\Data\My Documents\76335.cr3.Norgestimate-EE.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

c: **76334cr3.Norgestimate-EE.doc**

APPEARS THIS WAY
ON ORIGINAL

#4

CHEMISTRY REVIEW

ANDA #76-335

Norgestimate and Ethinyl Estradiol Tablets
0.250 mg/0.035 mg
0.215 mg/0.035 mg
0.180 mg/0.035 mg
(28-day regimen)

Andrx Pharmaceuticals, L.L.C.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA # **76-335**

2. REVIEW #: **04**

3. REVIEW DATE: December 19, 2003

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-27-2001
Amendment	11-22-2002
Bio amendment	12-12-2002
NC re change in ownership	01-06-2003
Gratuitous Amendment	03-25-2003
amendment	08-11-2003
FDA	
Bio review	FDA
NA letter	01-28-2003 acceptable
telecon to Andrx	07-23-2002
telecon to Andrx	Dec 5th 03
	Dec 10th 03

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	12-11-2003
tel. amendment	09. Dec 2003
tel amendment	10. Dec 2003

Chemistry Review Data Sheet

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, L.L.C.*

Address: 2945 West Corporate Lakes Blvd.
Weston, FL 33331

Representative: William Stahovec

Telephone: 954-358-6124 fax 954-358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: *n/a*
b) Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ; Oral-28 Day Regimen – NDA 19697) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-335: Norgestimate and Ethinyl Estradiol Tablets: **0.180 mg/0.035 mg and 0.215 mg/0.035 and 0.250 mg/0.035 mg (28 day).**

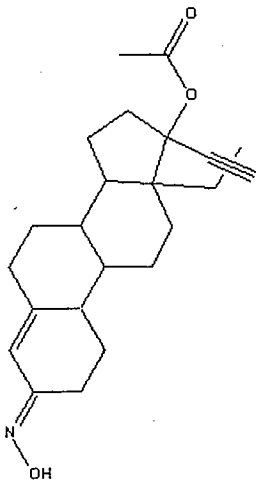
13. ROUTE of ADMINISTRATION: oral

14. R*x*/OTC DISPENSED: R*x*

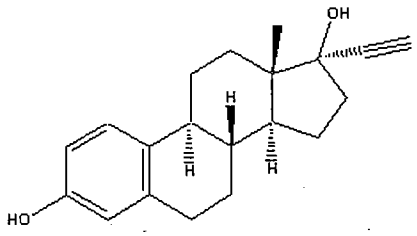
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

Norgestimate; [35189-28-7], $C_{23}H_{31}NO_3$ MW 369.5028



Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084



APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate	5-1-2002 Dr.Raw	NC to 5-23-03
	II			3	adequate	04-03-2003	"
	III			4	n/a		
	III			4	n/a		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

APPEARS THIS WAY
ON ORIGINAL

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Norgestimate and Ethinyl Estradiol Tablets	76-334	0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets	76-335	0.180 mg/0.035 mg and 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg / 0.035 mg ——28 day regimens)	75-804 [1st generic]	**0.250 mg/0.035 mg**
Norgestimate and Ethinyl Estradiol Tablets	75-808	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg —— 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	*n/a*		
EES	adequate	04-30-2003	
Methods Validation	n/a: non-complex DP		
Labeling	adequate	10-31-2003	D. Caterson
Bioequivalence	adequate	01-28-2003	N. Tran
Environ. Ass.	sat. CR1		
Radiopharmaceutical	*n/a*		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes If no, explain reason below:

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

30. MICROBIOLOGY: *n/a*

31. SAMPLES & RESULTS / METHODS VALIDATION STATUS: **n/a**
This is a non-complex drug product.

32. LABELING: **10-31-2003 acceptable**

33. ESTABLISHMENT INSPECTION: Overall *acceptable* 4/30/2003

34. BIOEQUIVALENCE: 01-28-2003 acceptable

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION: sat. **CR1**

cc: **ANDA 76-335**
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. / 12-19-03
HFD-623/ Dave S. Gill, Ph.D. / DSGill 12-22-03
HFD-617/Sarah Kim Park, Pharm. D. / for 12/30/03

F/T by /

V:\FIRMSAM\ANDRX\LTRS&REV\76335.cr4.Norgestimate-EE.doc

TYPE of LETTER: For TENTATIVE APPROVAL

V: Andrx\lets&rev\76335cr4.Norgestimate-EE.doc

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY PACKAGE	
ANDA #76-335 Firm: **Andrx**	Drug: Norgestimate and Ethinyl Estradiol Tablets Dosage: tabs Strength: 0.250 mg/0.035 mg; 0.215 mg/0.035 mg' 0.180 mg/0.035 mg (28-day regimen)
1. CGMP Statement/EIR Update Status:	EER status: Overall acceptable 4/30/2003
2. Bio Study:	01-28-2003 acceptable
3. Methods Validation – description of Dosage Form the same as the firm's:	n/a
4. Stability – Are Containers used in the Study Identical to those in the Container Section (#26)?:	Containers: sat. Identical?: yes
5. Labeling:	10-31-2003 acceptable
6. Sterilization Validation (if applicable):	n/a
7. Size of *Bio/Test Batch* (Firm's source of Bulk DS satisfactory?):	DMF # ——/acceptable Source: —— DMF # ——/acceptable. Source: ——
8. Size of Stability Batches (If different from bio batch were they mfg. *via* the same process?):	Size: ——— tabs each Same
9. Proposed Production Batch (Manufacturing process the same as Bio/Stability batch?):	Size: ——— tabs each Same
10. List of DP and DS specifications? Composition listed?	yes both
[signed at AP level]	1-2-04 *R.W. Trimmer*, Ph.D./12/09/03 *D.S. Gill*, Ph.D./12/22/03 DSG:jp 1-5-04

#5

CHEMISTRY REVIEW

ANDA #76-335

Norgestimate and Ethinyl Estradiol Tablets
0.250 mg/0.035 mg
0.215 mg/0.035 mg
0.180 mg/0.035 mg
(28-day regimen)

Andrx Pharmaceuticals, L.L.C.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA # **76-335**

2. REVIEW #: **05**

3. REVIEW DATE: March 19, 2004

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-27-2001
Amendment	11-22-2002
Bio amendment	12-12-2002
NC re change in ownership	01-06-2003
Gratuitous Amendment	03-25-2003
Amendment	08-11-2003
Amendment	11-12-2003
tel. amendment	09-12-2003
tel amendment	10-12-2003
FDA	FDA
Bio review	01-28-2003 acceptable
NA letter	07-23-2002
telecon to Andrx	Dec 5th 03
telecon to Andrx	Dec 10th 03
Fax to Andrx re tentative approval	Jan. 6th 04

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Minor amendment	Jan. 9th 04

Chemistry Review Data Sheet

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, L.L.C.*

Address: 4955 Orange Drive
Ft. Lauderdale, FL 33314

Representative: William Stahovec

Telephone: 954-358-6124 fax 954-358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: *n/a*
b) Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho-Tri Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ; Oral-28 Day Regimen – NDA 19697) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-335: Norgestimate and Ethinyl Estradiol Tablets: 0.180 mg/0.035 mg and 0.215 mg/0.035 and 0.250 mg/0.035 mg (28 day).

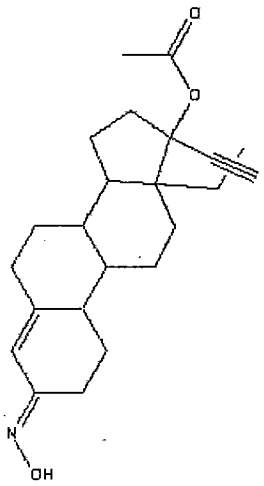
13. ROUTE of ADMINISTRATION: oral

14. R*x*/OTC DISPENSED: R*x*

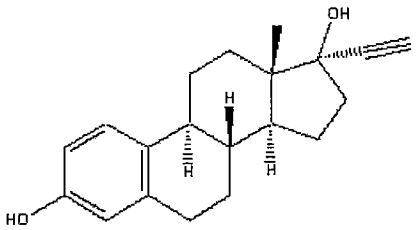
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

Norgestimate; [35189-28-7], $C_{23}H_{31}NO_3$ MW 369.5028



Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084



APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	**DATE REVIEW COMPLETED**	COMMENTS
	II			3	adequate	7-17-2003	NC to 3-18-03 per Dr. M.Darj
	II			1	adequate	03-18-2004	Amendment reviewed by Dr.RWTrimmer
	III			4	n/a		
	III			4	n/a		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Norgestimate and Ethinyl Estradiol Tablets	76-334	0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets	76-335	0.180 mg/0.035 mg and 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg / 0.035 mg ——— 28 day regimens)	75-804 [1st generic]	**0.250 mg/0.035 mg**
Norgestimate and Ethinyl Estradiol Tablets	75-808	0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg ——— 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	*n/a*		
EES	adequate	04-30-2003	
Methods Validation	n/a: non-complex DP		
Labeling	adequate	10-31-2003	D. Caterson
Bioequivalence	adequate	01-28-2003	N. Tran
Environ. Ass.	sat. CR1		
Radiopharmaceutical	*n/a*		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
No, we were just informed that patent issues that were holding up approval of this application are now out of the way.

Deficiencies: none

The Chemistry Review for ANDA 76-335

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommended for approval at this time.

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

n/a

II. Summary of Chemistry Assessments

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

Drug Product:

Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg

The listed reference drug product is **Ortho-Tri Cyclen®** (Norgestimate and ethinyl estradiol tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg Tablet; Oral-28 Day Regimen – NDA 19697) manufactured by Johnson RW. Andrx will market this drug product only in blisters at this time.

Drug Substances:

Norgestimate:

This is now a USP drug substance. It is a steroid which possesses antifertility and pregestatioal activity. It exists as an equilibrium mix of syn and anti isomers.

Ethinyl Estradiol:

A USP drug substance, a crystalline powder with a MW of 296.41 The firm uses the USP analytical method to monitor assay and their own method for monitoring impurities.

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

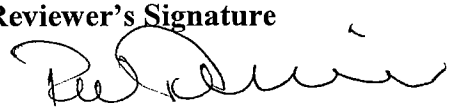
The labeling describes its use.

C. Basis for Approvability or Not-Approval Recommendation

Approvable due to satisfactory CMC. The Type II DMF's for the active ingredients are both adequate at this time.
Expiry of 18 months granted.

III. Administrative

A. Reviewer's Signature



B. Endorsement Block

ChemistName/Date:	Robert W. Trimmer, Ph.D./3/23/04
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./
ProjectManagerName/Date:	Sarah Kim Park, PM/3/25/04

3-25-04

C. CC Block

ANDA 76-335
ANDA dup
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Review of January 9th 2004 Minor Amendment.

Andrx states that there are no changes in the chemistry, manufacturing and controls data since the time of tentative approval.

The firm stated that they believe the application will be entitled to final approval on or after March 26, 2004 after the expiration of the pediatric exclusivity associated with the '839, '554. '006. and '051 patents.

Both Type II DMF's for the 2 active ingredients were checked for any changes and both remain adequate.

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information from

CHEMISTRY REVIEW #4

30. MICROBIOLOGY: *n/a*

31. SAMPLES & RESULTS / METHODS VALIDATION STATUS: **n/a**
This is a non-complex drug product.

32. LABELING: **10-31-2003 acceptable**

33. ESTABLISHMENT INSPECTION: Overall *acceptable* 4/30/2003

34. BIOEQUIVALENCE: 01-28-2003 acceptable

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION: sat. **CR1**

cc: **ANDA 76-335**
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. /3/23/04, Revised 3-25-04
HFD-623/ Dave S. Gill, Ph.D. /3/25/04 DS Gill 3-25-04
HFD-617/Sarah Park, Pharm. D. /3/25/04 3/25/04

F/T by: EW 3/25/04

C:\Data\My Documents\76335.cr5.Norgestimate-EE.doc

TYPE of LETTER: ~~For TENTATIVE~~ APPROVAL

V: Andrx\lets&rev\76335cr5.Norgestimate-EE.doc

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

BIOEQUIVALENCE REVIEW(S)

OCT 18 2002

Ethinyl Estradiol/Norgestimate
Tablets
0.035/0.180 mg, 0.035/0.215 mg, 0.035/0.250 mg
ANDA 76-335
Reviewer: Nhan L. Tran
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Andrx Pharmaceuticals
Lauderdale, FL 33314
Submission Date:
December 27, 2001

Review of Dissolution Data and a Waiver Request

BACKGROUND INFORMATION

Ethinyl Estradiol/Norgestimate (EE/NGM) is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. There are two products available from the innovator, RW Johnson: **Ortho Cyclen** (NDA 19-653) and **Ortho Tri-Cyclen** (NDA 19-697). **Ortho Cyclen** provides a 28-day regimen consisting of 21 days of **0.035 mg/0.250 mg** (EE/NGM) and 7 days of placebo. **Ortho Tri-Cyclen** provides a 28-day regimen consisting of 7 days of **0.035 mg/0.180 mg**, 7 days of **0.035 mg/0.215 mg**, 7 days of **0.035 mg/0.250 mg** and 7 days of placebo.

Andrx has submitted an ANDA 76-334 on December 27, 2001 comparing its EE/NGM (0.035mg/0.250 mg) with Ortho Cyclen 0.035 mg/0.250 mg, the reference listed drug (RLD) in the Orange Book. The firm has submitted a fasting study and dissolution data to support the ANDA. The fasting study and dissolution data were reviewed and found acceptable by the DBE. Based on the results of the study conducted in the ANDA 76-334 comparing Andrx's product, **0.035 mg/0.250 mg** tablets with RW Johnson's **Ortho Cyclen 0.035 mg/0.250 mg** tablets, the firm is submitting this ANDA 76-335 to request a waiver for its 0.035 mg/0.180 mg, 0.035 mg/0.215 mg and 0.035 mg/0.250 mg tablet strengths, a generic version of **Ortho Tri-Cyclen**.

In summary:

Ethinyl Estradiol/Norgestimate 0.035mg/0.250mg Tablets. RLD: Ortho Cyclen.	ANDA 76-334 (a generic version of Ortho Cyclen)	BE study results and dissolution data were submitted on 0.035mg/0.250mg tablet. In-vivo and in-vitro data were found acceptable by the DBE.
Ethinyl Estradiol/Norgestimate 0.035mg/0.180mg;0.035mg/0.215mg and 0.035mg/0.250mg Tablets. RLD: Ortho Tri-Cyclen.	ANDA 76-335 (a generic version of Ortho Tri-Cyclen)	Request waiver for 0.035mg/0.180mg; 0.035mg/0.215mg; 0.035mg/ 0.250mg tablets based on BE study in ANDA 76-334, formulation proportionality and dissolution data.

REVIEW HISTORY

This kind of cross ANDA reference was allowed by the Agency in the past as shown in the table below:

DOCUMENT	APPLICATION/FIRM	DESCRIPTION
Ethinyl Estradiol/Norgestimate Tablets, 0.035 mg /0.250 mg RLD Ortho Cyclen	75-804 Submitted: 3/16/2000 Barr.	A BE fasting study was conducted on Barr's 0.035 mg/0.250 mg tablet vs. Ortho Cyclen 0.035 mg/0.250 mg tablet.
Ethinyl Estradiol/Norgestimate 0.035mg/0.180mg;0.035mg/0.215mg and 0.035mg/0.250mg Tablets. RLD Ortho Tri-Cyclen	75-808 Submitted: 3/16/2000 Barr	Waiver for 0.035mg/0.018mg, 0.035mg/0.215mg, and 0.035 mg/0.250mg based on ANDA 75-804 was granted.
Ethinyl Estradiol/Norgestimate 0.035mg/0.180mg;0.035mg/0.215mg and 0.035mg/0.250mg Tablets.	OGD CD 00-091 Submitted: 3/8/00 [redacted]	DBE Recommendation: Fasting study on 0.035 mg/0.250 mg tablet, and waiver request on lower strengths.
Ethinyl Estradiol/Norgestimate 0.035mg/0.180mg;0.035mg/0.215mg and 0.035mg/0.250mg Tablets.	OGD CD 01-219 Submitted: 2/24/01 [redacted]	DBE Recommendation: Fasting study on 0.035 mg/0.250 mg tablet, and waiver request on lower strengths.
Ethinyl Estradiol/Norgestimate 0.035mg/0.180mg;0.035mg/0.215mg and 0.035mg/0.250mg Tablets.	OGD CD 01-225 Submitted: 4/30/01 Aspire Pharm	DBE Recommendation: Fasting study on 0.035 mg/0.250 mg tablet, and waiver request on lower strengths.

REVIEW OF THE WAIVER REQUEST

The firm submitted the formulation information and dissolution data to support the waiver request as follows:

1. **Formulation**:

Ingredients	0.180/0.035 mg	0.215/0.035 mg	0.250/0.035 mg
Norgestimate	0.180	0.215	0.250
Ethinyl Estradiol, USP	0.035	0.035	0.035
Pregelatinized Starch, NF			
Lactose Monohydrate, NF			
[redacted]			
FD&C Blue #1 HT			
Magnesium Stearate, NF			
Tablet Weight	**101.5**	**101.5**	**101.5**

All ingredients in the formulation are within the IIG's limits.

HOW SUPPLIED

For the innovator's products: ORTHO TRI-CYCLEN Tablets.

0.035 mg/0.180 mg tablet: **White** tablet, with "Ortho" and "180" debossed on each side.
0.035 mg/0.215 mg tablet: **Light blue** tablet, with "Ortho" and "215" debossed on each side.
0.035 mg/0.250 mg tablet: **Blue** tablet with "Ortho" and "250" debossed on each side.

For the test products:

0.035 mg/0.180 mg tablet: **White**, round, film coated tablets with Andrx logo on one side and **'746'** on other side.
0.035 mg/0.215 mg tablet: **Light blue**, round, film coated tablets with Andrx logo on one side and **'747'** on other side.
0.035 mg/0.250 mg tablet: **Blue**, round, film coated tabs w Andrx logo on one side and **'748'** on other side.

2. Dissolution Testing:

Currently there is no USP dissolution method for this combination product, and the firm has used the following method:

Medium: 900 mL of deionized water containing 500 PPM Tween® 20*
Apparatus: USP Apparatus 2 at 75 rpm
Temperature: 37 °C
Time Points: 10, 20, 30 and 45 minutes

**The concentration of 500 PPM of Tween 20, a viscous liquid, is same as 0.05% expressed in percentage v/v.*

The dissolution results are summarized in the Tables below:

Norgestimate: Dissolution for Test and Reference Products

Test: Ethinyl Estradiol and Norgestimate Dose: 0.035mg/0.25mg Lot # TB-021 **(Bio lot)** Reference: **Ortho Cyclen®** Dose: 0.035 mg/0.25 mg Lot # 10H006 **(Bio lot)** Assay methodology: HPLC						
Results of dissolution testing: **NORGESTIMATE**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	91		2.6	87		2.1
20	93		2.8	89		1.8
30	94		2.2	90		1.5
45	94		2.7	93		1.8
F2	74					
Test: Ethinyl Estradiol and Norgestimate Dose: 0.035mg/0.215mg Lot # TB-020 Reference: **Ortho Tri-Cyclen®** Dose: 0.035 mg/0.215 mg Lot # 20M214						
Results of dissolution testing: **NORGESTIMATE**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	86		2	79		7.3
20	89		1.6	93		4.3
30	91		1.8	95		3.7
45	92		1.5	96		3.7
F2	65					
Test: Ethinyl Estradiol and Norgestimate Dose: 0.035mg/0.180mg Lot # TB-019 Reference: **Ortho Tri-Cyclen®** Dose: 0.035mg/0.180mg Lot # 20M214						

Results of dissolution testing: **NORGESTIMATE**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	93		1.9	85		3.4
20	95		1.8	98		1.2
30	95		2	98		1
45	95		2.2	99		1.9
F2	65					

Ethinyl Estradiol: Dissolution for Test and Reference Products

Test: Ethinyl Estradiol and Norgestimate	Dose: 0.035mg/0.25mg	Lot # TB-021 **(Bio lot)**
Reference: **Ortho Cyclen®**	Dose: 0.035 mg/0.25 mg	Lot # 10H006 **(Bio lot)**

Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	95		2.8	101		1.1
20	95		2.5	101		1.4
30	95		2.6	101		1.5
45	96		2.6	100		1.6
F2	62					

Test: Ethinyl Estradiol and Norgestimate	Dose: 0.035mg/0.215mg	Lot # TB-020
Reference: **Ortho Tri-Cyclen®**	Dose: 0.035mg/0.215 mg	Lot # 20M214

Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	96		1.5	92		4.8
20	97		1.6	106		1.5
30	97		1.4	105		1.7
45	97		1.9	105		0.7
F2	56					

Test: Ethinyl Estradiol and Norgestimate	Dose: 0.035mg/0.180mg	Lot # TB-019
Reference: **Ortho Tri-Cyclen®**	Dose: 0.035mg/0.180mg	Lot # 20M214

Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	96		2.5	89		3.8
20	97		3.2	102		1.3
30	96		3.5	103		1.2
45	95		4.6	104		4.2
F2	57					

Comments on Dissolution:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies.

2. The Division has recently recommended the following interim dissolution testing method for ethinyl estradiol/norgestimate tablet, (ANDA 75-804, Barr Laboratories; ANDA 75-808, Barr Laboratories).

   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C

   The OGD Dissolution Database also recommends the following:
   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C

   The above method is the same as the one recommended for the NDA.

3. The firm's method uses **900 mL** of dissolution medium compared to **600 mL** as recommended in the FDA method. The firm's dissolution is, therefore, incomplete.

Recommendation

The comparative dissolution testing conducted by Andrx on its Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg, 0.035 mg/0.215 mg 0.035 mg/0.180 mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to Ortho Cyclen 0.035 mg/0.250 mg, Lot 10H006, Ortho Tri-Cyclen 0.035 mg/0.215 mg and 0.035 mg/0180 mg, Lot 20M214, is incomplete. The firm is advised resubmitting comparative dissolution testing using the following FDA recommended method:

Apparatus: USP, apparatus 2 (paddle), 75 rpm
Medium: **600 mL** of 0.05% Tween 20, at 37 °C
Sampling Times: 10, 20, 30 and 45 minutes.

Please include the mean, RSD, minimum and maximum (range) values and f2 in the report.

The firm should be informed of the above recommendation.

Nhan L. Tran, Ph.D.
Review Branch II

10/10/2002

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FT INITIALED SNerurkar

Concur
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-335 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Ethinyl Estradiol/Norgestimate Tablet, 0.035 mg/0.25 mg, 0.035 mg/0.215mg, 0.035 mg/0.180 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The comparative dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg, 0.035 mg/0.215 mg 0.035 mg/0.180 mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to Ortho Cyclen 0.035 mg/0.250 mg, Lot 10H006, Ortho Tri-Cyclen 0.035 mg/0.215 mg and 0.035 mg/0180 mg, Lot 20M214, is incomplete. You are advised to repeat comparative dissolution testing using the following FDA recommended method:

   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C
   Sampling Times: 10, 20, 30 and 45 minutes.

   Please include the mean, RSD, minimum and maximum (range) values and f2 in the report.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-335
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-655/Tran

Endorsements: (Draft and Final with Dates)
HFD-655/Tran
HFD-655/Nerurkar
HFD-650/Conner 10/18/02

10/10/02

V:\firmsam\Andrx\ltrs&rev\76335W1201.doc

BIOEQUIVALENCY – **Incomplete** Submission Dates: **12/27/2001**

Dissolution - **Incomplete**

1. **DISSOLUTION WAIVER** (DIW) Strengths: 0.035 mg/0.250 mg
Outcome: IC

2. **DISSOLUTION WAIVER** (DIW) Strengths: 0.035 mg/0.215 mg
Outcome: IC

3. **DISSOLUTION WAIVER** (DIW) Strengths: 0.035 mg/0.180 mg
Outcome: IC

Outcome Decisions:
IC - Incomplete

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

JAN 28 2003

Ethinyl Estradiol/Norgestimate Tablets
0.035/0.180mg, 0.035/0.215mg, 0.035/0.25mg
ANDA 76-335
Reviewer: Nhan L. Tran
V:\firmsam\Andrx\ltrs&rev\76335W1202.doc

Andrx Pharmaceuticals
Lauderdale, FL 33314
Submission Date:
December 12, 2002

Review of an Amendment (Dissolution Data)

OBJECTIVE

Review of Andrx Pharmaceuticals' amendment responding to the Agency's letter dated October 18, 2002. The firm was requested to repeat comparative dissolution testing using the following FDA recommended method:

Apparatus: USP, apparatus 2 (paddle), 75 rpm
Medium: **600 mL** of 0.05% Tween 20, at 37 °C
Sampling Times: 10, 20, 30 and 45 minutes.

Firm's Response:

The firm has provided comparative dissolution testing results on Ethinyl Estradiol/Norgestimate tablets, 0.035mg/0.25mg, 0.035mg/0.215mg, 0.035mg/0.180mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to Ortho Cyclen 0.035mg/0.25mg, Lot 10H006, Ortho Tri-Cyclen 0.035mg/0.215mg and 0.035mg/0180 mg, Lot 22A012 using the Agency's recommended method. The dissolution results are given in the table below:

Note: Both Ortho-Cyclen and Ortho-Tricyclen are 28-day packs. There are no corresponding 21-day packs.

Norgestimate

Test: Ethinyl Estradiol and Norgestimate Dose: 0.035mg/0.25mg Lot # TB-021 **(Bio lot)** Reference: **Ortho Cyclen®** Dose: 0.035mg/0.25mg Lot # 10H006 **(Bio lot)** Assay methodology: HPLC						
Results of dissolution testing: **NORGESTIMATE**						
Sampling	Test product			Reference Product		
Time (min)	Mean	Range	%CV	Mean	Range	%CV
10	90		3.1	101		1.8
20	91		3.1	100		1.7
30	92		2.7	98		1.9
45	93		2.7	99		2
Test: Ethinyl Estradiol and Norgestimate Dose: 0.035mg/0.215mg Lot # TB-020						

Reference: **Ortho Tri-Cyclen®**			Dose: 0.035mg/0.215mg			Lot # 22A012
Results of dissolution testing: **NORGESTIMATE**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	91		2	95		2.7
20	93		1.9	99		1.2
30	93		1.7	98		1.4
45	93		1.7	99		1.2
Test: Ethinyl Estradiol and Norgestimate			Dose: 0.035mg/0.180mg			Lot # TB-019
Reference: **Ortho Tri-Cyclen®**			Dose: 0.035mg/0.180mg			Lot # 22A012
Results of dissolution testing: **NORGESTIMATE**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	93		1.7	90		3.4
20	94		1.5	99		2
30	95		1.4	99		2.2
45	95		1.4	99		2

Ethinyl Estradiol

Test: Ethinyl Estradiol and Norgestimate			Dose: 0.035mg/0.25mg			Lot # TB-021 **(Bio lot)**
Reference: **Ortho Cyclen®**			Dose: 0.035mg/0.25mg			Lot # 10H006 **(Bio lot)**
Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	96		2.7	99		1.9
20	95		2.8	100		1.7
30	95		2.9	99		1.9
45	96		2.7	99		2.1
Test: Ethinyl Estradiol and Norgestimate			Dose: 0.035mg/0.215mg			Lot # TB-020
Reference: **Ortho Tri-Cyclen®**			Dose: 0.035mg/0.215 mg			Lot # 22A012
Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	93		1.8	100		3.1
20	94		1.5	103		1.3
30	94		1.6	103		1.3
45	94		1.7	103		1.3
Test: Ethinyl Estradiol and Norgestimate			Dose: 0.035mg/0.180mg			Lot # TB-019
Reference: **Ortho Tri-Cyclen®**			Dose: 0.035mg/0.180mg			Lot # 22A012
Results of dissolution testing: **ETHINYL ESTRADIOL**						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	95		2.1	94		3.5
20	95		1.8	103		1.5
30	96		2.3	103		1.7
45	95		1.7	103		1.5

Formulation:

Ingredients	0.180/0.035 mg	0.215/0.035 mg	0.25/0.035 mg
Norgestimate	0.180	0.215	0.25
Ethinyl Estradiol, USP	0.035	0.035	0.035
Pregelatinized Starch, NF			
Lactose Monohydrate, NF			
FD&C Blue #1 HT			
Magnesium Stearate, NF			
Tablet Weight	**101.5**	**101.5**	**101.5**

All ingredients in the formulation are within the IIG's limits.

Comments on Dissolution:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence study.

2. The firm has conducted dissolution testing using the Agency's recommended method, and the dissolution results meet the FDA specification. Firm's dissolution is acceptable.

RECOMMENDATIONS

1. The single-dose fasting bioequivalence study conducted by Andrx Pharmaceuticals in the ANDA 76-334 (monophasic) on its Ethinyl Estradiol; Norgestimate-28 Tablets 0.035mg/0.25mg, Lot # TB-021 comparing it to Ortho-Cyclen®-28 tablet, 0.035mg/0.25mg, Lot #10H006 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx Ethinyl Estradiol; Norgestimate-28 Tablet 0.035mg/0.25mg in the ANDA 76-335 (triphasic) are bioequivalent to the reference product 0.035mg/0.25mg tablet in Ortho-Cyclen®-28, manufactured by RW Johnson.

2. The comparative dissolution testing conducted by Andrx on its Ethinyl Estradiol/Norgestimate tablets, 0.035mg/0.25mg, 0.035mg/0.215mg 0.035mg/0.180mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to Ortho Cyclen 0.035mg/0.25mg, Lot 10H006, Ortho Tri-Cyclen 0.035mg/0.215mg and 0.035mg/0180 mg, Lot 22A012, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 600 mL of 0.05% Tween 20, at 37 °C using USP apparatus II (paddle) at 75 rpm. The test products should meet the following interim specification:

   NLT —% (Q) in 20 min for both components.

4. Since the formulations of Ethinyl Estradiol/Norgestimate tablets, 0.035mg/0.25mg, 0.035mg/0.215mg 0.035mg/0.180mg are proportionally similar, and the firm has met the in-

vivo and in-vitro requirements, the waiver request for its Ethinyl Estradiol/Norgestimate tablets, 0.035mg/0.215mg 0.035mg/0.180mg is granted under 21CFR320(22)(d)(2). Andrx's Ethinyl Estradiol/Norgestimate-28 tablets, 0.035mg/0.25mg, 0.035mg/0.215mg 0.035mg/0.180mg are bioequivalent to RW Johnson's Ortho Tri-Cyclen-28 0.035mg/0.25mg, 0.035mg/0.215mg and 0.035mg/0180mg tablets.

The firm should be informed of the above recommendations.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED SNerurkar 1/22/2003
FT INITIALED SNerurkar

Concur: 1/28/03
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-334 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCTS: Ethinyl Estradiol/Norgestimate tablets
0.035mg/0.25mg, 0.035mg/0.215mg,0.035mg/0.180mg.

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 600 mL of 0.05% Tween 20, at 37 °C using USP apparatus II (paddle) at 75 rpm. The test products should meet the following interim specification:

> Not less than — % (Q) of the labeled amounts of ethinyl estradiol and norgestimate are dissolved in 20 min.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-335
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-655/Tran

Endorsements: (Draft and Final with Dates)
HFD-655/Tran 1/22/03
HFD-655/Nerurkar
HFD-650/Conner 1/28/03

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BIOEQUIVALENCY – **Acceptable**
Dissolution - **Acceptable**

Submission Dates: **12/12/2002**

Study Amendment (STA)

Strength: 0.035mg/0.25mg, 0.035mg/0.215mg, 0.035mg/0.180mg

Outcome: **AC**

Outcome Decisions:

AC - Acceptable

- WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: **Ethinyl Estradiol/Norgestimate** ANDA # : 76-335
SPONSOR: Andrx Pharmaceuticals
DOSAGE FORM: Tablet
STRENGTH(S): **0.035/0.180mg, 0.035/0.215mg, 0.035/0.25mg**
TYPES OF STUDIES: NA
CLINICAL STUDY SITE(S): NA
ANALYTICAL SITE(S): NA

STUDY SUMMARY : NA

Waiver request is accepted per 21CFR 320.22(d)(3).

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility NA For cause NA Other	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Nhan L. Tran, Ph.D. BRANCH: II
INITIAL : _____ DATE : 1/24

TEAM LEADER : Shriniwas Nerurkar, Ph.D. BRANCH: II
INITIAL : _____ DATE : 1/22/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : _____ DATE : 1/28/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDAs 76-334 and 76-335 and the Minor Amendments dated August 11, and November 12, 2003.

The following deficiencies/comments were communicated to the firm.

1. Please provide stability data that support —%Q in 20 minutes dissolution time, as recommended by our Division of Bioequivalence. Your amendment dated October 11, 2003, page 116, gives —%Q in 30 minutes.

2. Your 18th month test station dissolution data should be provided assuming you are still seeking an 18 month expiry.

The firm stated that page 114 of the same amendment shows the stability data that is based on 20 minute dissolution time. The firm stated that they originally ran at 30 minutes for higher strength, then ran at 20 minutes. The firm stated that they do not have 18th month data at 20 minutes dissolution time.

The firm agreed to submit another test data at 24 months. The firm agreed to submit the updated stability data and provide a statement that the 22 MRT and 24 MRT data are at 20 minute dissolution time.

The firm's response may be submitted as a telephone amendment.

DATE
December 5, 2003

ANDA NUMBER
76-334 and 76-335

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
76-334
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (28-day regimen)

76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28-day regimen)

FIRM NAME
Andrx Pharmaceuticals, L.L.C.

FIRM'S REPRESENTATIVES:
Bill Stahovec
Larry Rosenthal (President)
Scott Roden (Vice President)

TELEPHONE NUMBER
954-358-6124

FDA REPRESENTATIVES:
Robert Trimmer 12-5-2003
Sarah Kim S. K 12/5/03

CC: T-Con Binder Log
ANDA 76-334 and 76-335
V:\FIRMSAM\ANDRX\TELECONS\76334.76335.tc.120503.doc

RECORD OF TELEPHONE CONVERSATION

Reference is made to the unapproved ANDAs 76-334 and 76-335 and the Minor Amendments dated August 11, and November 12, 2003. Reference is also made to the Telephone Amendment dated December 9, 2003.

The Agency stated that since the firm does not have 24 month test station dissolution data, the Agency will accept the 22 month test station.

The firm stated that they are still seeking the 18 month expiration date and stated that they will submit a revised stability report.

The firm's response may be submitted as a telephone amendment.

DATE
December 10, 2003

ANDA NUMBER
76-334 and 76-335

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
76-334
Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (28-day regimen)

76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28-day regimen)

FIRM NAME
Andrx Pharmaceuticals, L.L.C.

FIRM'S REPRESENTATIVES:
Bill Stahovec

TELEPHONE NUMBER
954-358-6124

FDA REPRESENTATIVES:
Robert Trimmer 12-19-03
Sarah Kim 12/19/03

CC: T-Con Binder Log
ANDA 76-334 and 76-335

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Division File

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-335 Applicant Andrx Pharmaceuticals L.L.C.
Drug Norgestimate and Ethinyl Estradiol Tablets Strength(s) 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg (28 day)

PROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 12/09 Initials MS

Date _____ Initials _____

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# _____
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☑
Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☑
Written request issued ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Study Submitted ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter: TA
Comments: PIII to All patents ped ext. will exp 3/26/2004

2. Project Manager, Sarah Kim Team 4
Review Support Branch

Date 12/23/03 Initials SK

Date 01/05/04 Initials SK

Original Rec'd date 12/31/2001
Date Acceptable for Filing 12/31/2001 ✓
Patent Certification (type) III
Date Patent/Exclus.expires 3/26/04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/30/2003
Date of Office Bio Review 1/28/03
Date of Labeling Approv. Sum 10/31/2003
Date of Sterility Assur. App. NIA
Methods Val. Samples Pending Yes ☐ No ☐ N/A
MV Commitment Rcd. from Firm Yes ☒ No ☐ Vol 1.1
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A
Previously reviewed and tentatively approved NO ☐ Date _____
Previously reviewed and CGMP def./NA Minor issued ☐ Date _____
Comments:

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 1/6/04 Initials RCC

The core section is satisfactory.

4. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review) N/A

Date _____ Initials _____

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date_____
Initials_____

RLD= Ortho Tri-Cyclen
Ortho McNeil Pharmaceutical, Inc.

NDA 19-697 (001)

6. Peter Rickman
Director, DLPS
Date 1/6/04
Initials RR

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 4/30/03 (Verified 1/6/04). No O.A.I. alerts noted. Bioequivalence waiver granted based upon acceptable biostudy conducted by Andrx under ANDA #76-334 on 0.25mg/0.035mg strength tablet, and acceptable dissolution data. (21 CFR ~~320~~ 320.22(d)(2). Office-level LOR endorsed 12/8/03. Labeling found acceptable for approval 10/31/03. Proprietary name, TRI-Previfem, found acceptable to DMETS on 10/8/02 and 7/1/03. This will need an update prior to final approval. CMC found acceptable 12/22/03. Methods validation request has been withdrawn (non-complex drug product) according to current ORS/OGD methods validation policy.

6. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 1/6/2004
Initials RLW

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: Andrx made paragraph III certifications to the '839, '554, '006, and '051 patents which were to expire on 9/26/03. However, on 12/18/03, the agency granted pediatric exclusivity to Ortho McNeil for Ortho Tri-Cyclen. Thus, the expiry of each of these patents has effectively been extended until 3/26/04. Andrx has updated its patent certification to reflect the new expiration date.

This ANDA is recommended for tentative approval.

7. Gary Buehler
Director, OGD
Date 1/6/04
Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Sarah Park
Review Support Branch
Date 1/06/04
Initials SP
☐ Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
11:33 Time notified of approval by phone 11:33 Time approval letter faxed
FDA Notification:
1/6/04 ~~11:33~~ Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/6/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou5.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76335 Applicant Andrx Pharmaceuticals
Drug Norgestimate / Ethinyl Estradiol tabs Strength(s) .250/.035 mg, .215/.035 mg, .180/.035 mg

PROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 25 March 04 Initials MMS	Date 3/26/04 Initials RW for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# 19-607,
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: PIII to '839, '554, '068, '051 patents
Patent expires 26 March ∴ Eligible for FA

2. Project Manager, Crayket Team 4 Review Support Branch	Date 3/25/04 Initials CW	Date Initials

Original Rec'd date 12/27/01
Date Acceptable for Filing 12/31/01
Patent Certification (type) III
Date Patent/Exclus.expires 3/26/04
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/30/03
Date of Office Bio Review 1/28/03
Date of Labeling Approv. Sum 10/31/03
Date of Sterility Assur. App. —
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐
Previously reviewed and tentatively approved ☒ Date 1/6/04
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:		Date 3/26/04 Initials

CMC satisfactory.

4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	**First Generics Only**	Date Initials

NA. Refer to Barr's ANDA 75-808 approved on 12/29/03 for this drug product. This ANDA was tentatively approved on January 6, 2004.

REVIEWER: **FINAL ACTION**

5. Gregg Davis
Deputy Dir., DLPS
Date _____
Initials _____

RLD= Ortho Tri-Cyclen Tablets NDA 19-697 (001)
Ortho McNeil Pharmaceutical, Inc.

6. Peter Rickman
Director, DLPS
Date 3/26/04
Initials PR for

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐

Comments: Acceptable EES dated 4/30/03 (Verified 3/26/04). No OAE alerts noted. Refer to the administrative sign-off form completed at the time of the tentative approval issued on 1/6/04. On 1/9/04, Andrx submitted a minor amendment to request final approval. Andrx stated that no changes had been made to the ANDA since the issuance of the TA letter. FPL remains acceptable. ODS/DHETS has also concurred via memo dated 1/7/04 that the proprietary name Tri-Previfem, remains acceptable. CMC found acceptable for final approval 3/25/04. Methods validation will not be requested - does not meet current criteria.

6. Robert L. West
Acting Deputy Director, OGD
Date 3/26/2004
Initials Robert L. West

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒

Comments: Andrx made paragraph III certifications to the '839, '554, '006, and '051 patents that were to have expired on September 26, 2003. However, the patents were effectively extended until March 26, 2004 upon the agency's granting of pediatric exclusivity to Ortho for Ortho Tri-Cyclen Tablets.

This ANDA is now recommended for final approval.

7. Gary Buehler
Director, OGD
Date 3/26/04
Initials GB

Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Review Support Branch Craig Kiester
Date 3/26/04
Initials CK

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

145 Time notified of approval by phone 150 Time approval letter faxed

FDA Notification:

3/26/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

3/26/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou5.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-335

CORRESPONDENCE

Andrx
PHARMACEUTICALS, INC.

2/26/02 Ack for filing 505(j)(2)(A) S. Middleton

December 27, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

#76-335

RE: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Gentlemen:

Andrx Pharmaceuticals, Inc. is submitting an Abbreviated New Drug Application under section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94, for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg. The reference-listed drug is RW Johnson's Ortho Tri-Cyclen® Tablets manufactured by Ortho-McNeil Pharmaceutical Inc.

This application contains the necessary information to demonstrate that Andrx's generic product is both pharmaceutically equivalent and bioequivalent to the reference listed drug. It is organized as suggested in the Guidance for Industry, Organization of and ANDA, issued February, 1999. The archival (blue) copy contains **3** volumes. The review copy is divided in two sections. The Chemistry Section (red) copy contains **3** volumes and the Bioequivalence Section (orange) copy contains **1** volume. An "Executive Summary" of this application follows this cover letter.

Andrx Pharmaceuticals commits to resolve any issues identified in the methods validation process after approval.

All correspondence should be addressed to Mr. William Stahovec, Associate Director of Regulatory Affairs, phone number (954) 585-1846, fax number (954) 584-1442.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 3 1 2001

Sincerely,

Diane Servello
Sr. Director, Regulatory Affairs

EXECUTIVE SUMMARY
Organization of the ANDA

Andrx Pharmaceuticals' ANDA for Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg consists of **3** volumes. It is organized according to the Office of Generic Drugs' February 1999 Guidance for Industry - Organization of an ANDA. Accordingly, it is divided into twenty-two sections designated I to XXII.

The entire ANDA is numbered sequentially, in the bottom center of each page, starting with the first page of the application form and continuing to the last page of the submission. Where this is not possible, the page numbers appears as close as possible to the bottom center or the most visible space. For ease of reference, a copy of the entire table of contents is found in each volume.

Two copies of the application are provided — one archival copy and one review copy (separated into bioequivalence and chemistry review sections). The archival (blue) copy contains all **3** volumes, the bioequivalence review (orange) copy contains **1** volume, and the chemistry review (red) copy contains **3** volumes as shown below:

Blue Archival copy - Volumes 1-3 (containing Sections I to XXII).
Orange Review copy -Volume 1 (containing Sections I to VII).
Red Review copy - Volumes 1-3 (containing Sections I to V, and VII to XXII).

Four identically numbered copies of the draft labels and labeling are provided in Section V.2. in both the archival copy and the chemistry copy. **THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA** – A 3.5" diskette with the package insert word processor file (Microsoft Word 97) is included in the chemistry review copy.

A Field Copy (burgundy) has been provided to the Orlando District Office.

Also note that two additional separately bound copies of Section XV containing the method validations of the drug product are provided.

II. Technical Summary

General:

The holder of this Abbreviated New Drug Application (ANDA) will be Andrx Pharmaceuticals, Inc., 4955 Orange Drive, Ft. Lauderdale, FL 33314.

The application is for a generic version of RW Johnson's Ortho Tri-Cyclen® brand of Norgestimate and Ethinyl Estradiol Tablets. As with Ortho Tri-Cyclen®28 Day Regimen, Andrx's Norgestimate and Ethinyl Estradiol Tablets will be available in package systems containing seven tablets of the 0.180 mg/0.035 mg strength, seven tablets of the 0.215 mg/0.035 mg strength, and seven tablets of the 0.250 mg/0.035 mg strength, and seven placebo tablets.

Please note that some of the documents submitted in this application have the name Aspire Pharmaceuticals, a subsidiary of Andrx Corporation. Development of the drug product was initiated by Aspire Pharmaceuticals, physically located within the campus of Andrx Pharmaceuticals, another subsidiary of Andrx Corporation. Prior to completion of product development and ANDA submission, Aspire Pharmaceuticals became part of Andrx Pharmaceuticals.

Basis for ANDA submission (Reference Listed Drug):

Ortho Tri-Cyclen®28 Day Regimen, Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg.

Patent certification and exclusivity information:

This ANDA contains a Paragraph III Certification and Exclusivity Statement covering any patents and exclusivities listed in the 21th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Andrx will not distribute the product until all listed patents and exclusivities expire.

Labeling:

Draft labeling is provided for Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, 0.215 mg/0.035mg and 0.250 mg/0.035 mg for blister packs of 28 tablets and 6 pack cartons. The labeling is the same as that for the reference listed drug, except where noted in the side-by-side comparisons in Section V.

Bioequivalence:

Andrx has conducted an *in vivo* bioequivalence study demonstrating that Andrx's Norgestimate and Ethinyl Estradiol tablets, 0.250 mg/0.035 mg is equivalent to the reference listed drug (Ortho-Cyclen® Tablets, 0.250 mg/0.035 mg). This study is included with our ANDA for our generic version of Ortho-Cyclen® , which is being submitted simultaneously with this ANDA.

Raw materials (drug substance and inactive ingredients):

[redacted]

All inactive ingredients used in the manufacture of Andrx's product are below the levels listed in the Inactive Ingredient Guide (IIG).

Manufacturing, testing, and packaging site:

The product described in this ANDA will be manufactured and tested at Andrx Pharmaceuticals, Inc., 4955 Orange Drive, Ft. Lauderdale, FL 33314. Testing of the raw materials, in-process materials, finished products, and stability samples will also be tested at this site or at approved outside firms. Packaging of the product will be performed by [redacted] (See Section X).

Manufacturing process:

[redacted]

ANDA test batches used in *in vivo* bioequivalence, *in vitro* comparative dissolution, and stability studies:

Norgestimate and Ethinyl Estradiol Tablets 0.180 mg/0.035 mg, **batch No. TB-019**
(Theoretical batch size: [redacted] tablets; Actual yield: [redacted])
Norgestimate and Ethinyl Estradiol Tablets 0.215 mg/0.035 mg, **batch No. TB-020**
(Theoretical batch size: [redacted] tablets; Actual yield: [redacted])
Norgestimate and Ethinyl Estradiol Tablets 0.250 mg/0.035 mg, **batch No. TB-021**
(Theoretical batch size: [redacted] tablets; Actual yield: [redacted])
Placebo, **batch No. TB-018** (Theoretical batch size: [redacted] tablets; Actual yield: [redacted])

Packaging:
The drug product will be available in blister packs of 28 tablets, (seven tablets of each strength and seven placebo tablets). The proposed container/closure system consists of a [redacted]

Analytical methods:

The analytical procedures for the drug substances are the current USP monographs or in-house methods validated by Andrx. The analytical methods for product release and stability testing program are based on the method in PF Vol. 26(5). A test for impurities and degradants was added to the product release and stability indicating procedures. Validation of these procedures is provided in Section XV. Two additional separately bound copies of Section XV are also submitted with this application.

Stability studies:

Stability studies have been initiated for the ANDA test batches in the container/closure system proposed for marketing. Stability data included in this ANDA are summarized in the table below.

Batch Number	Package Size	Accelerated data (40°C/75% RH)	Room Temperature data (25°C/60% RH)
TB-019 (0.180 mg/0.035 mg) TB-020 (0.215 mg/0.035 mg) TB-021 (0.250 mg/0.035 mg) TB-018 (Placebo)	Blister Pack	3 Months	3 Months

Based on the data provided in Section XVI, an expiration date of ——— is requested for this product.

ANDA 76-335

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Ft. Lauderdale, FL 33314

FEB 28 2002

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated February 25, 2002 and your correspondence dated February 25, 2002.

NAME OF DRUG: Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.25 mg/0.035 mg (28 Day)

DATE OF APPLICATION: December 27, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ruby Wu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-335
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB /Dreely 2/27/2002 date
HFD-615/SMiddleton, CSO _____ date
Word File
V:\FIRMSAM\ANDRX\LTRS&REV\76335.ACK
F/T EEH 02/27/02
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS, INC.

3/14/02
NDF
S. Middleton

March 5, 2002

Controlled Correspondence

Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: ANDA 76-335; Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg

Ms. Saundra Middleton:

As per your request, you will find enclosed a revised DMF letter from [redacted] allowing the Agency to have access to their Drug Master File No. [redacted]

Please direct any questions regarding to this application to William Stahovec, Associate Director of Regulatory Affairs, at (954) 585-1818 or (954) 358-6350 (fax)

Sincerely,
ANDRX PHARMACEUTICALS, INC.

Diane Sevello
Senior Director of Regulatory Affairs

RECEIVED
MAR 1 4 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS, INC.

ANDA 76-335
Norgestimate/Ethinyl Estradiol Tablets, 0.180/0.035 mg, 0.215/0.035 mg and 0.250/0.035 mg

July 17, 2002

Gary Buehler
Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

RE: LABELING AMENDMENT

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. has selected several brand names, which we would like to submit for consideration for the above-mentioned ANDA. The names we have selected are in order of the most preferred.

In this regard, we have enclosed the following:

1. Two computer generated black and white carton labels for each of the following names: Tri-Previfem and _____ (One copy is included with the archival copy and one copy is included with the review copy.)

Please advise us of the acceptability of these names. After your reply, we will submit final printed labeling reflecting the final accepted trade name. Should you have any questions, or comments, please contact me at (phone) 954-358-6114 or by fax at 954-358-6350.

Sincerely,
Andrx Pharmaceuticals, Inc.

Diane Servello
Director of Regulatory Affairs

RECEIVED
JUL 22 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

MINOR AMENDMENT

ANDA 76-335

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 23 2002

TO: APPLICANT: Andrx Pharmaceuticals, Inc.

TEL: 954-585-1846

ATTN: Diane Servello

FAX: ~~954-584-1442~~ 954-358-6350

FROM: Sarah Kim

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling and Bioequivalency comments will be provided under a separate cover.

SKm
7/23/02

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

7/23/2002 FDA FAX

5. Please provide a commitment to file the following information via a CBE-0 post-approval supplement when using the alternate manufacturing site for the drug substance: (a) comparative dissolution between the ANDA batch and the first batch of the drug product using the drug substance from the alternate site, (b) the first commercial batch of drug product, with a COA, using the drug substance from the alternate site on the long-term stability program, and (c) stability data table to indicate the drug substance site of manufacture.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

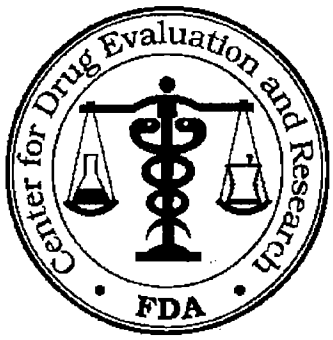
APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 76-335

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 23 2002



APPLICANT: Andrx

TEL: 954-585-1846

ATTN: Diane Servello

FAX: 954-584-1442

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 27, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1_ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

OCT 23 2009

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-335 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Ethinyl Estradiol/Norgestimate Tablet, 0.035 mg/0.25 mg, 0.035 mg/0.215mg, 0.035 mg/0.180 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The comparative dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg, 0.035 mg/0.215 mg 0.035 mg/0.180 mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to Ortho Cyclen 0.035 mg/0.250 mg, Lot 10H006, Ortho Tri-Cyclen 0.035 mg/0.215 mg and 0.035 mg/0180 mg, Lot 20M214, is incomplete. You are advised to repeat comparative dissolution testing using the following FDA recommended method:

   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C
   Sampling Times: 10, 20, 30 and 45 minutes.

   Please include the mean, RSD, minimum and maximum (range) values and f2 in the report.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Andrx™
PHARMACEUTICALS, INC.

MINOR AMENDMENT

November 22, 2002

ORIG AMENDMENT
N/am

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg Tablets

Gentlemen:

This letter is in response to your facsimile of July 23, 2002 (copy attached) regarding Andrx's ANDA 76-334, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg. In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the correspondence.

A. Chemistry Deficiencies:

Comment

1. Drug Master File # ——— is deficient. The holder of the DMF has been notified of the deficiencies. Please do not submit an amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

Response

——————— has submitted their response to the DMF deficiency on June 25, 2002. A copy of the cover letter submitted with the response is presented as **Exhibit 1**.

Comment

2. Regarding the inactive ingredients:

a. [redacted]

RECEIVED
NOV 2 5 2002
OGD / CDER

11-29-02

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Redacted 9 page(s)

of trade secret and/or

confidential commercial

information from

11/22/2002 ANDRX LETTER

Response to B1.

Andrx acknowledges that your Office of Compliance shall evaluate the cGMP compliance of all the facilities listed in our application and a satisfactory evaluation is required prior to the approval of this application.

Response to B2.

Andrx acknowledges that our bioequivalance information (including dissolution data), submitted in the June 27, 2002 Amendment, is pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

Response to B3.

Andrx acknowledges that method validation will be scheduled after testing issues in this letter are resolved.

Response to B4.

Andrx acknowledges that a review of the labels and labeling is pending. Any deficiencies found will be sent to us under separate cover.

Response to B5.

Andrx commits to file the following information via a CBE-0 post-approval supplement when using the alternate-manufacturing site for the drug substance:

a) comparative dissolution between the ANDA batch and the first batch of the drug product using the drug substance from the alternate site
b) the first commercial batch of drug product, with a COA, using the drug substance from the alternate site on long-term stability program
c) stability data table to indicate the drug substance site of manufacture.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Please direct any questions regarding this application to William Stahovec at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

Andrx™
PHARMACEUTICALS, INC.

BIOEQUIVALENCY AMENDMENT

December 12, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ORIG AMENDMENT
N/AB

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg

Gentlemen:

This letter is in response to your facsimile of October 23, 2002 (copy attached) regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg. In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the correspondence.

A. Bioequivalency Deficiency:

Comment

1. The comparative dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg, 0.035 mg/0.215 mg, 0.035 mg/0.180 mg, Lot #/TB-021, Lot #/TB-020 and Lot #/TB-019 respectively, compared to ortho Cyclen 0.035 mg/0.250 mg, Lot 10H006, Ortho Tri-Cyclen 0.035 mg/0.215 mg and 0.035 mg/0.180 mg, Lot 20M214, is incomplete. You are advised to repeat comparative dissolution testing using the following FDA recommended method:

   Apparatus: USP, apparatus 2 (paddles), 75 rpm
   Medium: 600 mL of 0.05% Tween 20, at 37 °C
   Sampling Times: 10, 20, 30 and 45 minutes

   Please include the mean, RSD, minimum and maximum (range) values and f2 in the report.

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4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Response
Comparative dissolution test results of Andrx's lot TB-021 and Ortho-Cyclen lot 10H006, including the mean, RSD, minimum and maximum (range) values and f2 are attached. Lot 10H006 was the lot used to demonstrate bioequivalence of Andrx's product. Ortho Tri-Cyclen lot 20M214 (including both 0.035 mg/0.180 mg and 0.035 mg/0.215 mg strengths) was not available for further testing. In its place, Lot 22A012 was tested against Andrx's product. Comparative dissolution test results for these and Andrx's lots TB-019 and TB-020 are also attached.

Please direct any questions regarding this application to William Stahovec at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Andrx™
PHARMACEUTICALS, INC.

January 6, 2003

Gary Buehler
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

Re: ANDA 76-335; Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg

Dear Mr. Buehler:

We refer to the abbreviated new drug application ("ANDA") listed above. Pursuant to §314.72, Andrx Pharmaceuticals, Inc. is notifying the agency of a change in ownership for this ANDA. The change in ownership is effective as of December 13, 2002.

All rights to this ANDA have been transferred to:

Andrx Pharmaceuticals L.L.C.
4955 Orange Avenue
Ft Lauderdale, FL 33314
Attention: William Stahovec, Associate Director of Regulatory Affairs
Phone: (954) 358-6100 or (954) 358-6124 (direct line)
Fax: (954) 358-6350

Andrx Pharmaceuticals, Inc. certifies that the new owner has a complete copy of this ANDA. A separate letter will be sent to your office by Andrx Pharmaceuticals, L.L.C. with a signed 356H form containing (1) a commitment to abide by the agreements, promises and conditions contained in this application; (2) the date the change in ownership is effective; and (3) a statement that a complete copy of the application is in their possession.

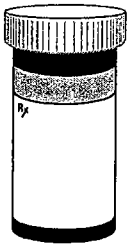
Please do not hesitate to contact me at (954) 585-1751 if you require additional information.

Sincerely,

Scott Lodin
Executive Vice President and General Counsel

RECEIVED
JAN 0 9 2003
OGD / CDER

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Jamie Rance
Andrx Pharmaceuticals, Inc.
Fax: 954-358-6350 **Phone:** 954-358-6108

From: Debra M. Catterson
Labeling Reviewer
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 38 **Date:** March 5, 2003
Comments:

Dear Ms. Rance,

Attached is the labeling review of your submissions dated December 27, 2001 and July 17, 2002 for ANDA 76-335 for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg.

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-335

Date of Submission: December 27, 2001 (Original) and July 17, 2002 (Amendment)

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg (28 day regimen)

Proprietary Name: Tri-Previfem™ Tablets

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   We have completed our nomenclature review and have no objection to the use of the proprietary name "Tri-Previfem™" for your drug product.

2. **CONTAINER** (Blister Pack Tablet Dispenser – 28 Day):
3. **CALENDAR LABEL STRIP** (To be affixed to the blister pack):
4. **CARDBOARD SLEEVE** (To contain the blister pack and calendar label strip):
5. **CARTON** (Box of 6 blister packs):

   Please refer to pages "0036-40" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions.

6. **PROFESSIONAL PACKAGE INSERT**:

   Please refer to pages "0043-48, 0050-51, 0053, 0056-57, 0059, 0061-64, 0069, 0071-72, 0076, 0079-81, and 0083" of the attached mocked-up copy of your draft insert labeling for all of the requested labeling revisions:

7. **BRIEF SUMMARY PATIENT PACKAGE INSERT**:

   Please refer to pages "0087, 0089, and 0093-96" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions:

8. **DETAILED PATIENT LABELING INSERT**:

   Please refer to page "0071-72, 0076, 0079-81, and 0083" of the attached mocked-up copy of your draft labeling for all of the requested labeling revisions:

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Mocked-up copy of the firm's draft labeling.

APPEARS THIS WAY
ON ORIGINAL

35 pages of draft labeling have been removed from this portion of the document.

3/5/2003 FDA FAX

76-335 (2-1)

ANDA (See Attachment)

Andrx Pharmaceuticals, L.L.C.
Attention: William Stahovec
4955 Orange Avenue
Ft. Lauderdale, FL 33314

MAR 17 20

Dear Sir:

We acknowledge receipt of your communications dated January 6, 2003, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug applications (ANDA) for the drug products listed in the attachment.

Your letter details the transfer of ownership of the ANDAs from Andrx Pharmaceuticals, Inc. to Andrx Pharmaceuticals, L.C.C.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending applications.

The material submitted is being retained as part of your applications.

Sincerely yours,

William P. Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

CC: ANDA (See Attachment)
Division File
Field Copy
HFD-92
HFD-610/Wm. Rickman

Endorsement:
HFD-617/T. Palat, Branch PM, 3/17/03 2/27/03 date
HFD-617/T. Ames, Chief, RSB 3/17/03 3/13/03 date
Nw\02\27\03V:\FIRMSAM\ANDRX\LTRS&REV\40441tra.own.mult..doc
F/T by KW/3/14/03

TRANSFER OF OWNERSHIP!

APPEARS THIS WAY
ON ORIGINAL

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3/17/2003 FDA LETTER (ATTACHMENT)

Andrx
PHARMACEUTICALS
LLC

GRATUITOUS AMENDMENT

March 25, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ORIG AMENDMENT
N/AA

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.18 mg/0.035 mg (28 day)

Gentlemen:

Please refer to Andrx Pharmaceuticals' abbreviated new drug application for Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.18 mg/0.035 mg (28 day). Pursuant to 21 CFR § 314.96, Andrx herewith submits an amendment providing for an additional packaging site. The proposed packaging site is ——— facility at ——— ——— This is being submitted as a Gratuitous Amendment.

Please note that the ANDA was originally submitted by Andrx Pharmaceuticals, Inc. Ownership of the ANDA was later transferred to Andrx Pharmaceuticals, LLC, a Delaware LLC. Andrx notified the agency of this change in ownership of the ANDA in a letter dated January 6, 2003.

In support of this amendment, Andrx states and /or certifies the following:

1) The facility has a current and satisfactory cGMP compliance profile with the FDA for the type of packaging operation in question. Their last inspection was———.

2) ——— facility is in conformance with cGMPs. Signed cGMP and GDEA certifications are attached.

3) Andrx commits to place at least the first production batch on long-term stability using the approved protocol and submitting the resulting data in the annual report.

Andrx Pharmaceuticals, LLC certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

RECEIVED
MAR 26 2003
OGD / CDER

Andrx
PHARMACEUTICALS
LLC

Please direct any questions regarding this application to me at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Andrx
PHARMACEUTICALS
LLC

76-
ANDA ~~#75~~-335
TRI-PREVIFEM™ (norgestimate and ethinyl estradiol)

May 1, 2003

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Amendment – Labeling

Dear Mr. Buehler:

Reference is made to the FDA facsimile dated March 5, 2003 regarding labeling comments for the above application.

In this regard, we have enclosed the following:

1. Twelve copies of blister card. (Six copies are included with the archival copy and six copies are included with the review copy.)
2. Twelve copies of blister card sleeve. (Six copies are included with the archival copy and six copies are included with the review copy.)
3. Twelve copies of blister card calendar strip. (Six copies are included with the archival copy and six copies are included with the review copy.)
4. Twelve copies of carton. (Six copies are included with the archival copy and six copies are included with the review copy.)
5. Twelve copies of prescribing information. (Six copies are included with the archival copy and six copies are included with the review copy.)
6. Twelve copies of detailed patient labeling and brief summary package insert combination. (Six copies are included with the archival copy and six copies are included with the review copy.)
7. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the labeling, annotating the revisions is included.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6124.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

RECEIVED
MAY 5 - 2003
OGD / CDER

William Stahovec
Assoc. Director Regulatory Affairs

cc: Debbie Catterson (Desk Copy Room N140)

MINOR AMENDMENT

ANDA 76-335

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 1 2003

TO: APPLICANT: Andrx Pharmaceuticals, L.L.C. TEL: 954-358-6124

ATTN: William Stahovec FAX: 954-358-6350

FROM: Sarah Kim PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.35 mg and 0.250 mg/0.035 mg (28 day regimen).

Reference is also made to your amendment(s) dated: November 22, 2002 and March 25, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry and Bioequivalency comments provided. Labeling comments will be provided under separate cover.

SKM
6/30/03

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7/1/2003 FDA FAX

e. Please provide 3 months of accelerated stability data that support the 20 minute dissolution time (recommended by our Division of Bioequivalence).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

2. Please provide updated stability data for all strengths for the drug product.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-334 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCTS: Ethinyl Estradiol/Norgestimate tablets
0.035mg/0.25mg, 0.035mg/0.215mg,0.035mg/0.180mg.

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 600 mL of 0.05% Tween 20, at 37 °C using USP apparatus II (paddle) at 75 rpm. The test products should meet the following interim specification:

> Not less than —% (Q) of the labeled amounts of ethinyl estradiol and norgestimate are dissolved in 20 min.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Andrx
PHARMACEUTICALS
LLC

MINOR AMENDMENT

August 11, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ORIG AMENDMENT
N/am

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

Gentlemen:

This letter is in response to your facsimile of July 1, 2003 (copy attached) regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the correspondence.

Please note that the ANDA was originally submitted by Andrx Pharmaceuticals, Inc. Andrx notified the agency of the change in ownership of the ANDA to Andrx Pharmaceuticals LLC, a Delaware LLC, in a letter dated January 6, 2003.

A. Chemistry Deficiencies:

Comment

1.

Response

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8/11/2003 ANDRX LETTER

Response to 6e
As per our telephone call with Dave Gill on July 8, 2003, Andrx will be submitting dissolution data from testing of CRT stability samples pulled at 22 MRT. Dissolution data is presented as Exhibit 9.

B. Additional Comments

1. A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

Response
Andrx acknowledges that any deficiencies found in the labeling will be sent under separate cover.

2. Please provide updated stability data for all strengths for the drug product.

Response
The latest stability data is provided in Exhibit 10. Based on the latest room temperature data, Andrx is requesting an 18 months expiration period for this product. In addition, a revised stability protocol is provided in Exhibit 11.

Please note that Andrx has revised its ———— specification for placebo tablets back to ————. A copy of the revised test method and specification is provided as Exhibit 12.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Please direct any questions regarding this application to William Stahovec at (954) 358-6124, email at william.stahovec@andrx.com, or fax at (954) 358-6350, or Tony Amann, Executive Vice President of Scientific Affairs, at (954) 358-6132.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

MINOR AMENDMENT

ANDA 76-335

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 15 2003

TO: APPLICANT: Andrx Pharmaceuticals, L.L.C. TEL: 954-358-6124

ATTN: William Stahovec FAX: 954-358-6350

FROM: Sarah Kim PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28 day regimen).

Reference is also made to your amendment(s) dated: August 11, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments will be provided under separate cover.

10/15/03

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10/15/2003 FDA FAX

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

DSG,M

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

10-15-03

APPEARS THIS WAY
ON ORIGINAL

Andrx
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MINOR AMENDMENT

November 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ORIG AMENDMENT
N/AM

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

Gentlemen:

This letter is in response to your facsimile of October 15, 2003 (copy attached) regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, LLC is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the correspondence.

Please note that the ANDA was originally submitted by Andrx Pharmaceuticals, Inc. Andrx notified the agency of the change in ownership of the ANDA to Andrx Pharmaceuticals LLC, a Delaware LLC, in a letter dated January 6, 2003.

A. Chemistry Deficiencies:

Comment

1. [ ]

Response

The limit for ———————————————————). A copy of the revised specification is provided in Exhibit 1.

Comment

2. [ ]

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11-19

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

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11/12/2003 ANDRX LETTER

Andrx Pharmaceuticals, LLC certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Please direct any questions regarding this application to William Stahovec at (954) 358-6124, email at william.stahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Fax Cover Sheet

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Jamie Rance
Andrx Pharmaceuticals, Inc.
Fax: 954-358-6350 **Phone:** 954-358-6108

From: Debra M. Catterson
Labeling Reviewer
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 11 **Date:** November 13, 2003
Comments:

Dear Ms. Rance,

Please refer to the attached mocked-up copy of your sleeve, carton, and insert labeling for all of the requested labeling revisions from my review of your submission dated May 1, 2003 for ANDA 76-335 for Norgestimate and Ethinyl Estradiol Tablets (Triphasic Regimen).

These revisions are "post-approval" revisions, which can be made at the time of next printing and submitted in an annual report provided the changes are described in full. We refer you to 21 CFR 314.81(b)(2)(iii) for guidance.

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

10 pages of draft labeling have been removed from this portion of the document.

11/13/2003 FDA FAX

Andrx
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LLC

December 9, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ORIG AMENDMENT
N/A M

Attn: Ms. Sara Kim

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

Dear Ms. Kim:

This letter is in response to your telephone calls of December 5, 2003 and December 9, 2003 regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

In the teleconference of December 5, 2003, Andrx agreed to supply additional dissolution data to support the requested 18 month expiration of the drug product. However, it is not possible to test the 24 month CRT stability samples as intended. The samples were pulled and tested at 22 months and results were already reported in the stability reports. There are no more of these tablets remaining. There are some remaining 18 month CRT tablets for the 0.215 mg/0.035 mg and 0.25 mg/0.035 mg strengths. These have been in the laboratory for 10 months. In addition, there are tablets packaged in blister packs remaining from the exhibit batch that have been stored in the warehouse under controlled conditions required by cGMPs, but not necessarily at 25°C±2°C and 60% ± 5% relative humidity. For the 0.18 mg/0.035 mg strength, all that remain are the samples stored in the warehouse.

Please let us know if the additional dissolution data requested can be obtained by testing any of these samples.

If you have any questions, do not hesitate to contact me at (954) 358-6124, email at william.stahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

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Andrx
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TELEPHONE AMENDMENT

December 11, 2003

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

Gentlemen:

This letter is in response to our teleconference of December 5, 2003 regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, LLC is submitting a telephone amendment to this ANDA that provides a complete response to all the deficiencies discussed during the teleconference.

Please note that the ANDA was originally submitted by Andrx Pharmaceuticals, Inc. Andrx notified the agency of the change in ownership of the ANDA to Andrx Pharmaceuticals LLC, a Delaware LLC, in a letter dated January 6, 2003.

A. Chemistry Deficiencies:

Comment

Submit revised stability reports clearly indicating dissolution parameters at the time the dissolution test was performed.

Response

The stability reports were revised accordingly. Please note there were three different sets of dissolution parameters listed in the reports. All other parameters being the same, the differences are noted below:

1. Volume 900 mL, Dissolution Time 30 minutes (Initial to 6 months)
2. Volume 600 mL, Dissolution Time 30 minutes (9 months to 18 months)
3. Volume 600 mL, Dissolution Time 20 minutes (22 months)

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DEC 12 2003
OGD/CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx regrets the confusion caused by the previous stability reports. Copies of the revised reports are attached.

Comment
Submit dissolution data from the 24 month CRT stability samples

Response
As discussed by phone on December 10, 2003, due to there being no remaining tablets from the 24 month CRT stability samples, the Agency will accept the 22 month CRT data previously submitted to support the requested 18 month product expiration. Please refer to the attached revised stability reports.

Comment
Repeat your request for an 18 month expiration period for this product.

Response
Andrx requests an 18 month expiration period for this product based on the submitted real time stability data.

Andrx Pharmaceuticals, LLC certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Please direct any questions regarding this application to me at (954) 358-6124, email at william.stahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

4-1

Andrx
PHARMACEUTICALS
LLC

MINOR AMENDMENT
FINAL APPROVAL REQUESTED

January 9, 2004

ORIG AMENDMENT N/AM

NAI
Request for final approval.
1/15/04

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

RE: ANDA 76-335
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen).

Dear Mr. Buehler:

This letter is in response to your facsimile of January 6, 2004 (copy attached) regarding Andrx's ANDA 76-335, Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.25 mg/0.035 mg (28 day regimen) granting the application tentative approval. In accordance with the tentative approval letter, Andrx Pharmaceuticals, LLC is submitting a minor amendment requesting final approval of the ANDA.

The ANDA was originally submitted December 27, 2001 and accepted for filing December 31, 2001. It included a paragraph III certification for patent # 4,530,839 (the '839 patent), patent # 4,544,554 (the '554 patent), patent # 4,461,006 (the '006 patent), and patent # 4,628,051 (the '051 patent).

We believe the application will be entitled to final approval on or after March 26, 2004 after the expiration of the pediatric exclusivity associated with the '839, '554, '006, and '051 patents.

There are no changes in the chemistry, manufacturing and controls data in the application since the tentative approval.

Please direct any questions regarding this application to me at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Associate Director of Regulatory Affairs

RECEIVED
JAN 12 2004
OGD/CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054