CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-334

Name: Previfem Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg)

Sponsor: Andrx Pharmaceuticals, LLC

Approval Date: January 9, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

APPROVAL LETTER

ANDA 76-334

JAN 9 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 Previfem Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg), packaged in 28-day cycle regimens.

Reference is also made to your amendments dated June 27, and July 17, 2002; and May 1, November 12, November 17, December 9, and December 10, 2003.

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 Previfem Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ortho Cyclen-28® Tablets, 0.25 mg/0.035 mg, of Ortho McNeil Pharmaceutical, Inc.). 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
Director
1/9/04
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-334
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 30 Dec 03
HFD-617/S.Park/ for 12/30/03
HFD-613/D.Catterson/ Debra M. Catterson 12/31/03
HFD-613/J.Grace/ 12/31/2003

12/26 and 1/6/04

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F/T by

APPROVAL

Robert Lyn West
1/6/2004
pending DHETS update
of OK for proprietary
name.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

APPROVED LABELING

PREVIFEM™
(norgestimate and ethinyl estradiol)

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

PREVIFEM™
(norgestimate and ethinyl estradiol)

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

PREVIFEM™
(norgestimate and ethinyl estradiol)

PRESCRIBING INFORMATION

℞ Only

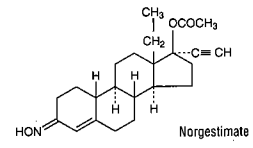
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

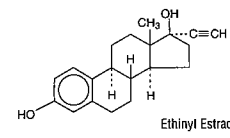
PREVIFEM™ Tablets are a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

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 PREVIFEM™. 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

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

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 PERCENTAGECONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	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 clinical trials with norgestimate and ethinyl estradiol tablets, 1,651 subjects completed 24,272 cycles and a total of 18 pregnancies were reported. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 0.96 per 100 women-years. This rate includes patients who did not take the drug correctly.

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

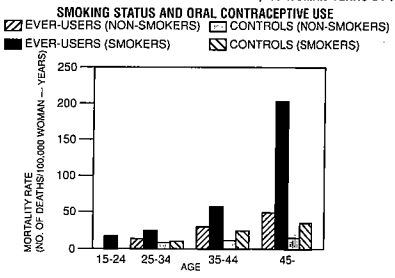


TABLE II. (Adapted from P.M. Layde and V. Beral, ref. #12.)

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 III**). 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 III: 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.[35-44,79-89]

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 [52-54,95] 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 PREVIFEM™ Tablets there were no clinically significant changes in fasting blood glucose levels. No statistically significant changes in mean fasting blood glucose levels were observed 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] It should be noted that in two separate large clinical trials (N = 633 and N = 911), no statistically significant changes in mean blood pressure were observed with PREVIFEM™ Tablets.

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, PREVIFEM™ Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. 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 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 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 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 **PRECAUTIONS** 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 consecutiveperiods, pregnancy should be ruled out before continuing oral contraceptive use.

HOW SUPPLIED
PREVIFEM™ Tablets (norgestimate and ethinyl estradiol) are available in a blister pack tablet dispenser (NDC 62037-751-28) containing 28 tablets: 21 blue tablets and 7 teal tablets containing inert ingredients. 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 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) [see USP Controlled Room Temperature.]; 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. 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 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.

PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. 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.

PREVIFEM™ Tablets: 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

PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. 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" blue pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" teal pills (without hormones).

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. 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" blue 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" blue 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** 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** 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** 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.

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: 10/03

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(norgestimate and ethinyl estradiol)

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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

See reverse side for additional information.

DETAILED PATIENT LABELING (continued)

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
PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. 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" blue pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" teal pills (without hormones).

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. 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" blue 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" blue 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** 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** 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** 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.

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: 10/03

7308

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.

PREVIFEM™ Tablets (norgestimate and 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. 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 noncontraceptive 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.

PREVIFEM™ Tablets (like all oral contraceptives) are intended to prevent pregnancy. 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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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. 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" blue 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" blue 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** 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** 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:

See reverse side for additional information.

BRIEF SUMMARY PATIENT PACKAGE INSERT (continued)

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** 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 Tablet 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 controls 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: Discard calendar label.

Day 1 Start: Place label strip, 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 pack is empty,
- You will start a new pack on the day after pill "28".

9
THE FIRST PILL IN EVERY PACK 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 PACK – 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 in Week 1 or Week 2 of your pack:
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 two pills in **Week 2** or **Week 3** or if you miss two pills in a row in **Week 3** or if you miss three or more pills in a row during the first 3 weeks:
Keep taking one pill each day until Sunday.
*On Sunday, **THROW OUT** the rest of the pills and start a new pack.*

☐ **Day 1 Start** ✎

a. If you miss two pills in a row of pills in Week 1 or Week 2 of your pack:
Take two pills as soon as you remember and two pills the next day, then keep taking one pill each as usual.

b. If you miss two pills in Week 2 or Week 3 or if you miss two pills in a row **in Week 3** or if you miss three or more pills in a row during the first 3 weeks:
***THROW OUT** the rest of the pills and start a new pack that day.*

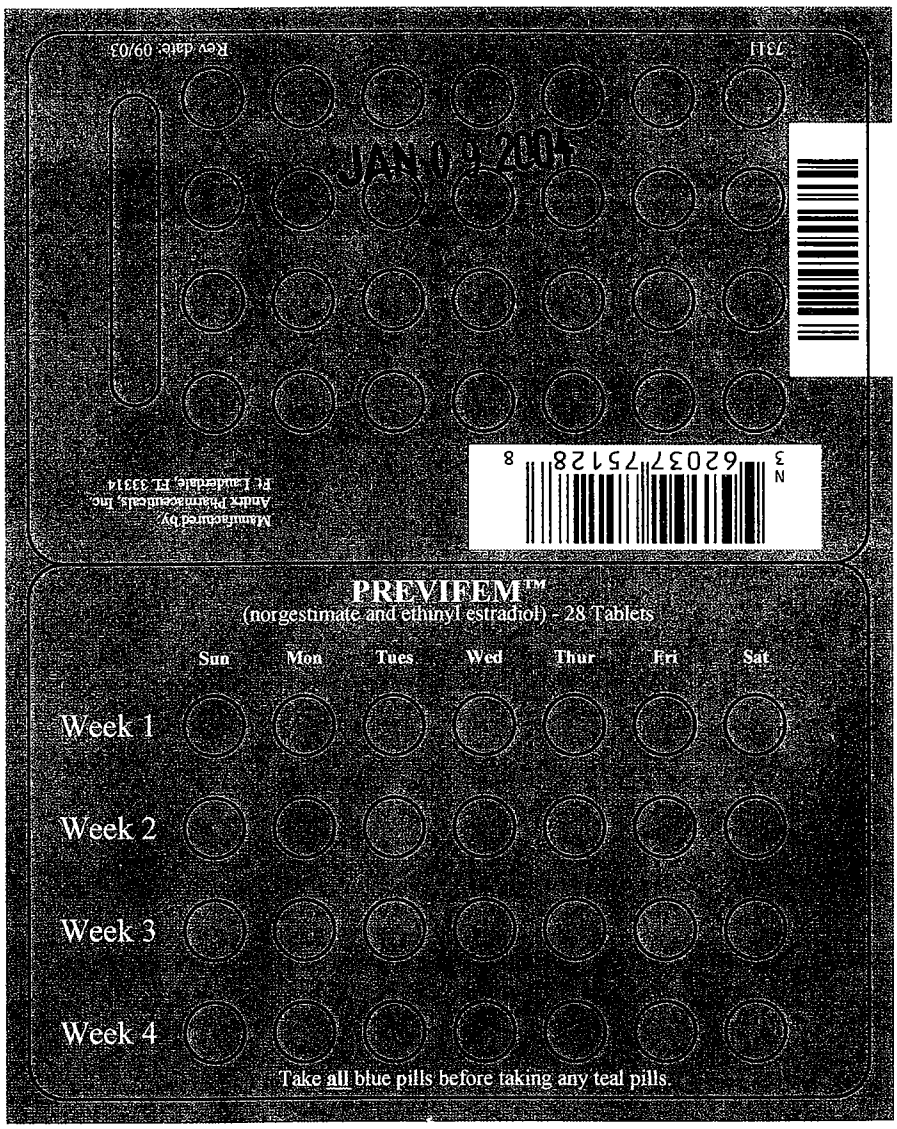
If you miss pills in Week 4...
Remember that pills **in Week 4** are "reminder" pills and do not contain active ingredients.
- If you miss any pills in Week 4, you will still be protected:
Throw away the missed pills and keep taking one pill each day until you finish the pack. Start a new pack on the day after the last pill.

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: 10/03 7309

ANDA #76-334
PREVIFEM™
(norgestimate [0.25 mg]
and ethinyl estradiol [0.035 mg])Tablets
FINAL PRINTED LABELING



NDA-334

76-334

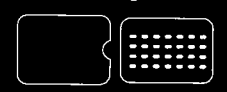
NDC 62037-751-28

6 Blister Packs 28 Day Regimen

Previfem™

(norgestimate and ethinyl estradiol)

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



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) [see USP Controlled Room Temperature.]; excursions permitted to 15° - 30° C (59° - 86° F).

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

6 Blister Packs 28 Day Regimen

Previfem™
(norgestimate and 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 sleeve 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.
Ft. Lauderdale, FL 33314
www.andrx.com

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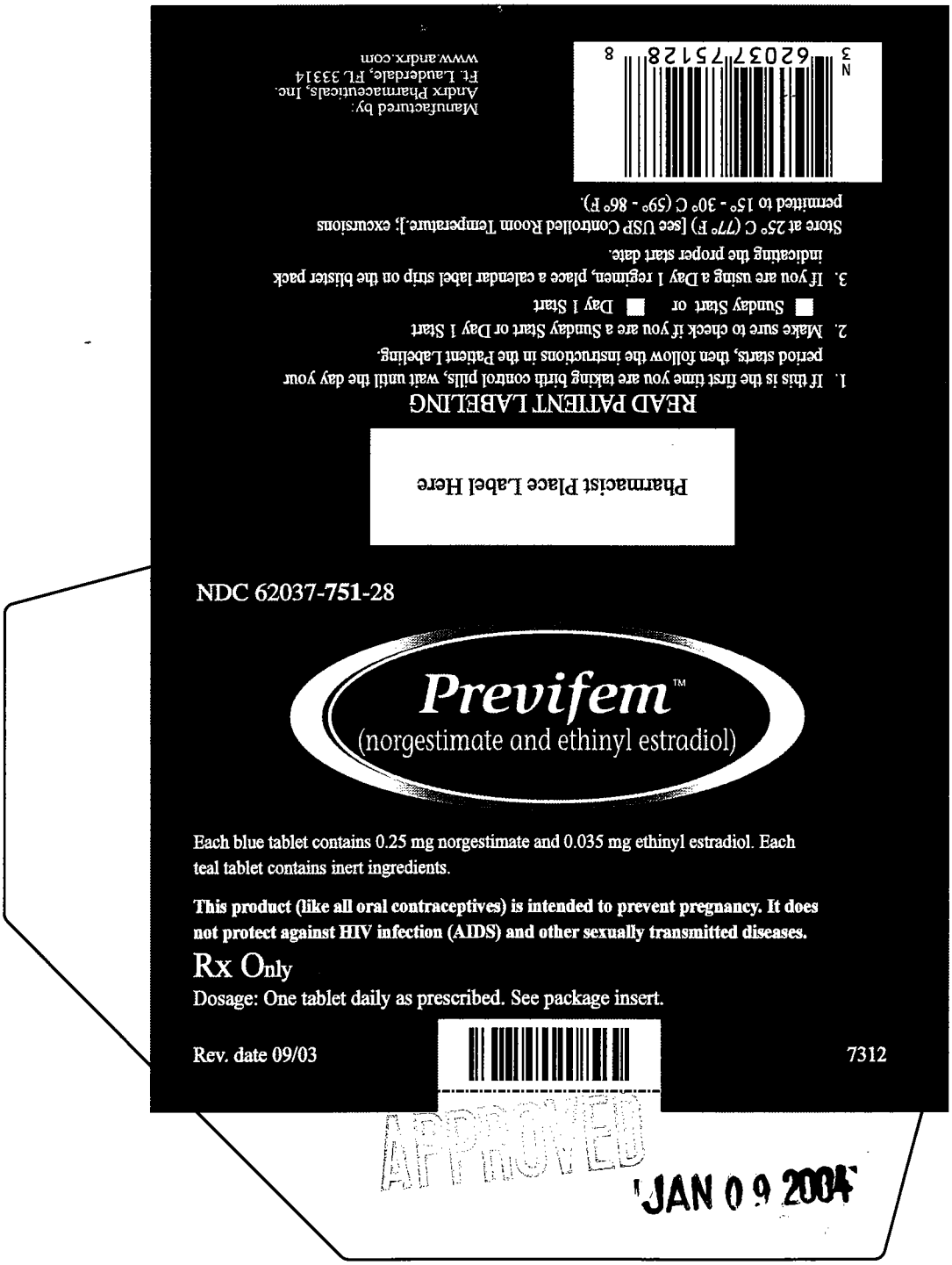
JAN 09 2004


Previfem™
(norgestimate and ethinyl estradiol)
Contains: 6 Blister Packs,
28 Tablets Each and
6 Label Strips
6 Blister Packs 28 Day Regimen
NDC 62037-751-28
6 Blister Packs 28 Day Regimen
Previfem™
(norgestimate and ethinyl estradiol)
Contains: 6 Blister Packs,
28 Tablets Each and
6 Label Strips
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) [see USP Controlled Room Temperature.]; excursions permitted to 15° - 30° C (59° - 86° F).
Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314
www.andrx.com
Rev. date 09/03 7314
6 Blister Packs 28 Day Regimen
Previfem™
(norgestimate and 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.
Ft. Lauderdale, FL 33314
www.andrx.com
Lot:
Exp:

76-334

ANDA #76-334
PREVIFEM™
(norgestimate [0.25 mg]
and ethinyl estradiol [0.035 mg])Tablets
FINAL PRINTED LABELING



HOW TO USE THIS BLISTER PACK

APPROVED JAN 09 2004

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

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

7313

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

LABELING REVIEW(S)

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

ANDA Number: 76-334

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, 0.25 mg/0.035 mg (28 day regimen)

Proprietary Name: Previfem™ Tablets

2.1

Labeling Deficiencies:

1. **GENERAL COMMENT:**

We have completed our nomenclature review and have no objection to the use of the proprietary name "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 "0032 - 0036" 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 "0039-43, 0045-48, 0051-53, 0056-58, 0065-66, 0070, 0073-75, and 0077" 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 "0081, 0083, and 0087-90" 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 "0092" 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 in final print.

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.

_34_ 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 "Previfem™" was found acceptable by DMETS on October 8, 2002 (Consult #02-0159)**	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. **NONE.**		X	

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Ortho-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-653/S-025; revised January 2000 and approved June 5, 2000; and S-027, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

   Exclusivity Data– NDA 19-653

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. 0372.]

4. CONTAINER/CLOSURE

   Blister Film: [redacted] clear transparent plastic film.
   Blister Backing: [redacted] push thru Aluminum Foil with [redacted]

   [Vol. A1.3 pg. 0687-698.]

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. 0258.]

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. 0698.]

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. 0152.]

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. 0115.]

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:

"active" 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 tablet.
[Vol. A1.3 pg. 0719 and 0733.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on September 16, 2002, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Previfem™ " for their product. DMETS concluded on October 8, 2002, that "Previfem" was an acceptable name for this drug product (Consult #02-0159).

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

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 3/4/03

Team Leader: John Grace Date:

John J Grace 3/5/2003

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cc:

ANDA: 76-334
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

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

ANDA Number: 76-334

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

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

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

Proprietary Name: Previfem™ Tablets

Labeling Deficiencies:

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

   Satisfactory in final print.

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

   Refer to the attached mocked-up copy of your labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.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 labeling.

_2_ 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 "Previfem™" was found acceptable by DMETS on October 8, 2002 (Consult #02-0159). 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 #02-0159-1). However, "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. **NONE.**		X	

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-653/S-025; revised January 2000 and approved June 5, 2000; and S-027, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-653

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. 0372.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted]

[Vol. A1.3 pg. 0687-698.]

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. 0258.]

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. 0698.]

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. 0152.]

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. 0115.]

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:

"active" 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."
[Vol. A1.3 pg. 0719 and 0733.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on September 16, 2002, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Previfem™ " for their product. DMETS concluded on October 8, 2002, that "Previfem" was an acceptable name for this drug product (Consult #02-0159). 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 #02-0159-1). However, "Previfem" will need another re-review from DMETS, since it has been over 90 days since the final OK was given.

Date of Review: 10/28/03 Date of Submission: 5/01/03

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 10/31/03
Team Leader: John Grace Date:
John Grace 10/31/2003

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cc:
ANDA: 76-334
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\andrx\ltrs&rev\76334NA2.L.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 76-334

Date of Submission: November 17, 2003 (Amendment – FPL)

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

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

Proprietary Name: 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 November 17, 2003 submission. [Vol. 5.1, Rev. date: 09/03]

CALENDAR LABEL STRIP (To be affixed to the blister pack):
Satisfactory as of the November 17, 2003 submission. [Vol. 5.1, Rev. date: 03/03]

CARDBOARD SLEEVE (To contain the blister pack and calendar label strip):
Satisfactory as of the November 17, 2003 submission. [Vol. 5.1, Rev. date: 09/03]

CARTON (Box of 6 blister packs):
Satisfactory as of the November 17, 2003 submission. [Vol. 5.1, Rev. date: 09/03]

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the November 17, 2003 submission. [Vol. 5.1, Rev. date: 10/03]

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT:
Satisfactory as of the November 17, 2003 submission. [Vol. 5.1, Rev. date: 10/03]

Revisions needed post-approval: None.

Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-653

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-CYCLEN® Tablets

NDA Number: 19-653

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-653/S-025: Approved June 5, 2000; and S-027 (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 "Previfem™" was found acceptable by DMETS on October 8, 2002 (Consult #02-0159). 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 #02-0159-1). However, "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. **NONE.**		X	

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Ortho-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-653/S-025; revised January 2000 and approved June 5, 2000; and S-027, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

   Exclusivity Data– NDA 19-653

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. 0372.]

4. CONTAINER/CLOSURE

Blister Film: [redacted] clear transparent plastic film.
Blister Backing: [redacted] push thru Aluminum Foil with [redacted]

[Vol. A1.3 pg. 0687-698.]

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. 0258.]

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. 0698.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at 25°C (77°F) [see USP Controlled Room Temperature]; excursions permitted to 15°- 30°C (59°- 86°F).
[Vol. A1.1 pg. 0152.]

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. 0115.]

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:

"active" 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. 0719 and 0733.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on September 16, 2002, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Previfem™ " for their product. DMETS concluded on October 8, 2002, that "Previfem" was an acceptable name for this drug product (Consult #02-0159). 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 #02-0159-1). However, "Previfem" will need another re-review from DMETS, since it has been over 90 days since the final OK was given.

Date of Review: 11/25/03 Date of Submission: 11/17/03

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 11/25/03

Team Leader: John Grace Date:

John J Grace 11/26/03

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cc:

ANDA: 76-334
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\andrx\ltrs&rev\76334APL.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

CHEMISTRY REVIEW(S)

ANDA #76-334

Norgestimate and Ethinyl Estradiol Tablets 0.250 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 #**76-334**

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
76-334	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

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-Cyclen®-28** (Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg; Oral-28 Day Regimen – NDA 19653) manufactured by Johnson RW.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-334: Norgestimate and Ethinyl Estradiol Tablets: **0.250 mg/0.035 mg**

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

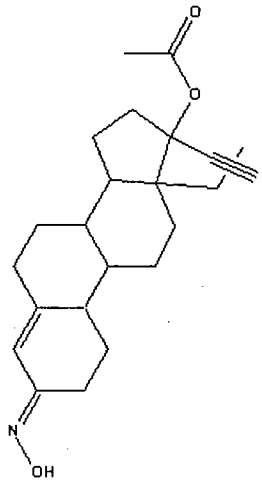
14. Rx/OTC DISPENSED: Rx

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

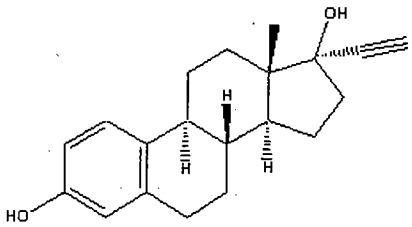
__x__ Not a SPOTS product

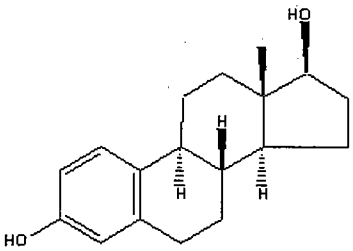
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

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

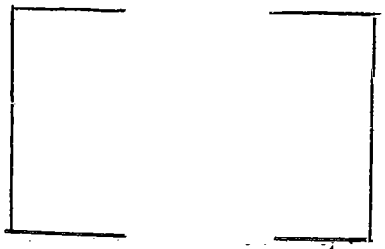


Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084





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	05-01-2002	by ARaw
	II			1	not adequate	05-24-2002/ issued 2.June	by 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)

Commitment Needed:
More than one manufacturing site exists in this one DMF —— . The applicant uses the material from site one to support the exhibit batch (bio batch) and must provide the following commitment for the site two.
An acceptable EER for both the sites was already found.

Three comparative COA's for drug substance manufactured at both the sites.

Place first batch of drug product (strength used to support bio study) using drug substance from site two on a 3 month accelerated stability program.

Comparative dissolution data between the bio batch strength and the first batch of DP (strength used to support bio study) using DS from site two.

Place the first commercial batch of each strength on long-term stability program.
A stability data table to indicate the DS site of manufacture.

This change can be filed as CBE-0 post-approval supplement.

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 (21 and 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 (21 and 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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-334/76-334

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./ 7-12-02
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./ 7/18/02 for
ProjectManagerName/Date:	Ruby Wu, PM/

C. CC Block

ANDA 76-334
ANDA dup
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APPEARS THIS WAY
ON ORIGINAL

Redacted 34 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

8. [redacted]

9.

10.

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

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Your bioequivalence information (including dissolution data), submitted in the June 27, 2002 Amendment, are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

3. Please note that methods validation will be scheduled after testing issues in this letter are resolved.

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

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 7/23/02

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

cc: ANDA 76-334
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

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

HFD-623/ Upinder Atwal for Dave S. Gill, Ph.D. /7/18/02 7/20/02 for

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

F/T by gp/7/19/02

V:\FIRMSam\Andrx\ltrs&rev**76334cr1.Norgestimate-EE.**doc

TYPE of LETTER: NOT APPROVABLE - MINOR

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

ANDA #76-334

Norgestimate and Ethinyl Estradiol Tablets

0.250 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 # **76-334**

2. REVIEW #: **2**

3. REVIEW DATE: May 30, 2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27. Dec. 2001

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Minor Amendment	22. Nov. 2002

7. NAME & ADDRESS of APPLICANT:

Name: *Andrx Pharmaceuticals, Inc.*

Address: 4955 Orange Drive
Fort 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 Cyclen®-28** (Norgestimate and Ethinyl Estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-28 Day Regimen – NDA 19653) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-334: Norgestimate and Ethinyl Estradiol Tablets: **0.250 mg/0.035 mg**

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

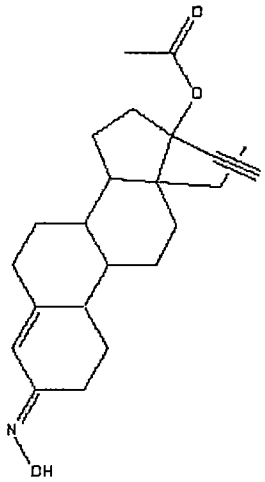
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

x Not a SPOTS product

APPEARS THIS WAY
ON ORIGINAL

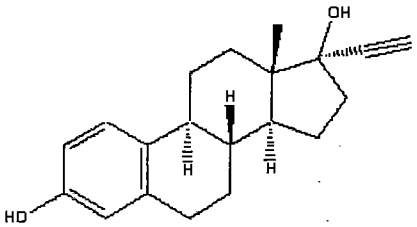
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

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

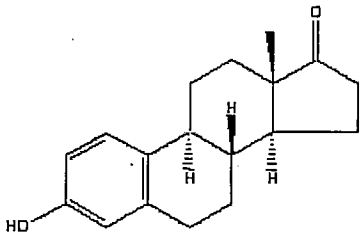


APPEARS THIS WAY
ON ORIGINAL

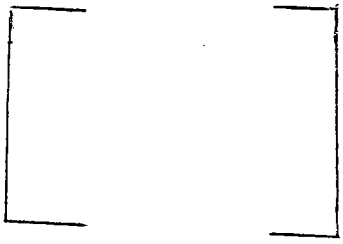
Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084



Estradiol



and [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	05-01-2002	by ARaw
	II			1	adequate	04-03-2003	by 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 (21 and 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 (21 and 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	n/a	n/a	
EES	adequate	24.Dec.2002	
Methods Validation	need only for DP awaiting revision		
Labeling	pending		D.Catterson
Bioequivalence	adequate	9-16-02	Chaurasia
Environ. Assoc.	sat	n/a	
Radiopharmaceutical	n/a	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:

APPEARS THIS WAY
ON ORIGINAL

Redacted 42 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #2

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

1. Please provide updated stability data using the updated new impurity specifications.

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

Sincerely yours,

Paul Schwegler 6/3/03

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
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

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

HFD-623/ Dave S. Gill, Ph.D. /6/10/03 DSGill 6-16-03

HFD-617/S. Kim, Pharm. D. /6/10/03 for 6/16/03

F/T by /sk/06-11-03 /ard/6/11/03

V:\FIRMSAM***Andrx**\ltrs&rev**76334cr2.Norges-EE.tabs.**doc

TYPE of LETTER: NOT APPROVABLE - MINOR

c: **76334cr2.Norges-EE.tabs.doc**

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

ANDA #76-334

Norgestimate and Ethinyl Estradiol Tablets

0.250 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

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA # **76-334**

2. REVIEW #: **3**

3. REVIEW DATE: September 24, 2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27. Dec. 2001
Amendment	22. Nov. 2002

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Minor Amendment	11.August 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

CHEMISTRY REVIEW

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho Cyclen®-28** (Norgestimate and Ethinyl Estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-28 Day Regimen – NDA 19653) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-334: Norgestimate and Ethinyl Estradiol Tablets: **0.250 mg/0.035 mg**

13. ROUTE of ADMINISTRATION: oral

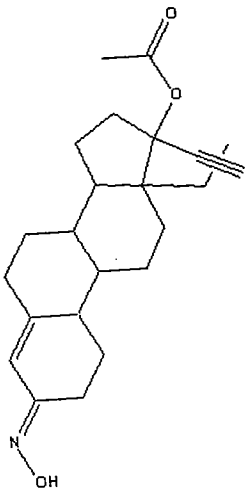
14. Rx/OTC DISPENSED: Rx

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

x Not a SPOTS product

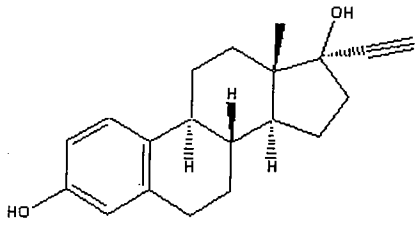
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLE. FORM, & MW:

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

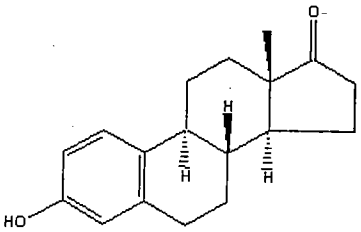


Executive Summary Section

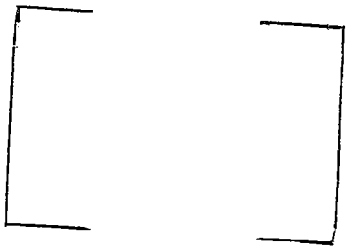
Ethinyl Estradiol: $C_{20}H_{24}O_2$, MW 296.4084



Estradiol



and ——— an impurity



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	07-18-2003	no changes (amendments or AR's) to Aug. 27th
	II			1	adequate	04-03-2003	no changes (amendments or AR's) Aug. 27th
	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 (21 and 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 (21 and 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a	n/a	
EES	adequate	24.Dec.2002	
Methods Validation	need only for DP awaiting revision		
Labeling	pending		D.Catterson
Bioequivalence	adequate	9-16-02	C. Chaurasia
Environ. Assoc.	sat	n/a	
Radiopharmaceutical	n/a	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:

APPEARS THIS WAY
ON ORIGINAL

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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

cc: ANDA
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 DSGill 10-15-03

HFD-617/S. Kim, Pharm. D. /10/9/03 10/15/03

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

V:\FIRMSAM*Andrx*\ltrs&rev\76334cr3.Norges-EE.tabs.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

ANDA #76-334

Norgestimate and Ethinyl Estradiol Tablets

0.250 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

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA # **76-334**

2. REVIEW #: **4**

3. REVIEW DATE: December 19, 2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27. Dec. 2001
Amendment	22. Nov. 2002
Amendment	11. August 2003
telecon to Andrx	05. December 03
telecon to Andrx	10. December 03

6. SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Document Dates
amendment	12. November 2003
tel. amendment	09. December 2003
tel amendment	10. December 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

CHEMISTRY REVIEW

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS for SUBMISSION:

The listed reference drug product is **Ortho Cyclen®-28** (Norgestimate and Ethinyl Estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-28 Day Regimen – NDA 19653) manufactured by Ortho McNeil Pharmaceuticals, Inc.

10. PHARMACOL. CATEGORY: prevention of pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY:

76-334: Norgestimate and Ethinyl Estradiol Tablets: **0.250 mg/0.035 mg**

13. ROUTE of ADMINISTRATION: oral

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

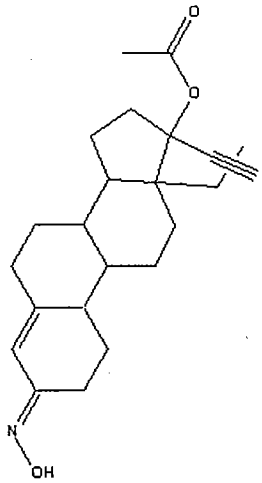
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

x Not a SPOTS product

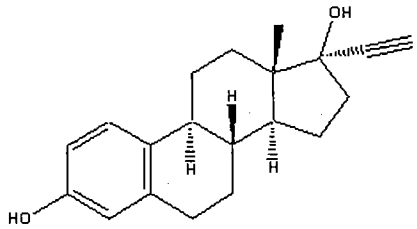
APPEARS THIS WAY
ON ORIGINAL

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



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMF's:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate	07-18-2003	no changes (amendments or AR's) to present
	II			3	adequate	04-03-2003	no changes (amendments or AR's) to present
	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 (21 and 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 (21 and 28 day regimens)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	n/a	n/a	
EES	adequate	29.Dec.2002	
Methods Validation	n/a		
Labeling	adequate	11-26-03	
Bioequivalence	adequate	9-16-02	
Environ. Assoc.	sat	n/a	
Radiopharmaceutical	n/a	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:

APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #4

30. MICROBIOLOGY: n/a

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

32. **LABELING: adequate 11/26/03**

33. **ESTABLISHMENT INSPECTION:** Overall *acceptable* as of 29.Dec.2002

34. **BIOEQUIVALENCE:** Acceptable 9/16/02

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

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA
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\76334cr4.Norges-EE.tabs.doc

TYPE of LETTER: For APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

BIOEQUIVALENCE REVIEW(S)

Ethinyl Estradiol and Norgestimate Tablet-28
0.035 mg/0.25 mg
ANDA 76-334
Reviewer: Chandra S. Chaurasia
V:\firmsam\Andrx\ltrs&rev\76334N1201.doc

Andrx Pharmaceuticals, Inc.
Lauderdale, FL 33314
Submission Date: December 27, 2001

Review of a Bioequivalence Study and Dissolution Data

INTRODUCTION:

Ortho Cyclen® (Ethinyl Estradiol; Norgestimate) is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. It is available in 21-day and 28-day dosage regimens.

Reference Listed Drug:
Ortho Cyclen -21, manufactured by RW Johnson, Strength: 0.035 mg; 0.25 mg, Application Number: 019653, Approval Date: DEC 29, 1989 is listed as the RLD in the Orange Book. Each of the 21 blue tablets contains 0.035 mg of the estrogenic compound ethinyl estradiol (EE) and 0.250 mg of the progestational compound norgestimate (NGM).

Ortho Cyclen-28 manufactured by RW Johnson Strength: 0.035 mg:0.25 mg Application Number: 019653, Approval Date: DEC 29, 1989. This is not listed as an RLD in the the Orange Book (Electronic 2002). Each of the 21 blue tablets contains 0.035 mg of the estrogenic compound ethinyl estradiol (EE) and 0.250 mg of the progestational compound norgestimate (NGM). Each of the 7 placebo green tablets contains inert ingredients: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch

First Generic: No
Type of Submission: Original ANDA

Contents of Submission:
1. Fasting study
2. Dissolution data

Recommended Dose: The dosage of Ortho Cyclen -28, 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 green tablet daily for 7 days.

BACKGROUND

Pharmacokinetics and Metabolism:
Norgestimate and ethinyl estradiol are well absorbed following oral administration of Ortho Cyclen. 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 radiolabelled norgestimate. These include various hydroxylated metabolites and conjugates of these metabolites.

Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

HISTORICAL INFORMATION

I. In recent Control Documents (99-147: ————, Submission Date 4/9/99; 00-133: ————, Submission Date 03/08/2000; 01-225: Aspire Pharmaceuticals, Submission Date: 4/30/01) pertaining to BE of ethinyl estradiol and norgestimate, the firms were advised of the following:

   1) Conduct one bioequivalence study on Ortho Cyclen®-21 or Ortho-Cyclen®-28, and request waivers for Ortho Cyclen®-28 or Ortho-Cyclen®-21 under the fasting conditions. Since, the labeling for Ortho-Cyclen® does not mention any food effect, a non-fasting study is not necessary.

   2) According to the *Guidance for Industry: Bioavailability and Bioequivalence of Orally Administered Drug Products – General considerations* (October 2000), only ethinyl estradiol and norgestimate are necessary to analyze.

II. In a recent submission from Barr Laboratories' generic versions of Ortho Cyclen®-21 and Ortho Cyclen®-28 (ANDA 75-804, Letter Date 3/16/00), a bioequivalence fasting study was conducted on 0.035 mg/ 0.25 mg Ethinyl Estradiol/Norgestimate-28 day tablet comparing it with Ortho-Cylen-28 tablet. The bioequivalence study was found to be acceptable, and a biowaiver on the 21-day product was granted based on the bio study on the 28-day product, and on dissolution data.

   In the above ANDA, PK analyses were based upon measurements of 17-Deacetyl norgestimate and ethinyl estradiol, although the firm had also submitted statistical data on levo-norgestrel. It is further noted that in a recent control correspondence

with ———— (OGD 01-219, Submission Date: 2/24/01), the Division provided the following recommendations:

1. To measure the ethinyl estradiol and 17-Deacetyl norgestimate for establishing BE of Ortho Cyclen® product.

2. To conduct a two-way crossover, single-dose fasting bioequivalence study on generic Ortho Cyclen®-21 Dialpak® tablets, and request waivers for generic version of Ortho Cyclen®-28. A non-fasting biostudy is not necessary for this drug product.

Protocol No. PRACS R01-287: A Relative Bioavailability Study of Ethinyl Estradiol/Norgestimate Tablets under Fasting Conditions.

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	————
Principal Investigator:	———— , Pharm. D.
Clinical Study Dates:	Initiated on 08/11/ 2001, Completed on 11/06/2001
Analytical Facility	Norgestimate: ————
	Ethinyl Estradiol: ————
Analytical Section Heads:	————
Analytical Study Dates:	17-Deacetyl Norgestimate: 11/01/2001 to 12/04/2001 (Vol. 1.2, pp. 1324). Ethinyl Estradiol: 10/22/2001 to 11/15/2001 (Vol. 1.3, pp. 2082).
Storage Period:	17-Deacetyl Norgestimate: 116 days. Ethinyl Estradiol: 97 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Norgestimate/Ethinyl estradiol	ORTHO-CYCLEN®
Manufacturer:	Aspire Pharmaceuticals, Inc.*	Ortho-McNeil Pharm.
Manufacture Date:	06/2001	N/A
Expiration Date:	N/A	06/03
ANDA Batch Size:	————	N/A
Batch/Lot Number:	TB-021	10H006
Potency:		
Norgestimate:	97.5%	102.4%
Ethinyl estradiol:	97.8%	99.9%
Content Uniformity:		
Norgestimate:	98.9% (RSD=2.8%)	104.7% (RSD=0.6%)
Ethinyl estradiol:	100.0% (RSD=3.3%)	104.2% (RSD=0.7%)
Strength:	0.250 mg/0.035	0.250 mg/0.035
Dosage Form:	Tablet	Tablet
Dose Administered:	0.500 mg/0.070 mg (1x2 tabs)	0.500 mg/0.070 mg (1x2 tabs)
Study Condition:	fasting	Fasting
Length of Fasting:	10 hours	10 hours

*A Subsidiary of Andrx Pharmaceuticals, Inc.

Randomization		Design	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	See Dose Administration*

***Dose Administration** occurred either on Day 2, Day 3, or Day 4 of two consecutive menstrual cycles (where Day 1 represented the onset of menstruation). The washout period between doses was the length of each subject's menstrual cycle: details of dose administration for each individual subject are provided in Vol. 1.4, pp. 2608-2611.

Randomization Scheme: **AB:** 2, 3, 5, 6,7, 8, 9, 10,12, 15,18, 19, 20, 26, 29
BA: 1, 4, 11,13, 14,16, 17, 21, 22, 23, 24, 25,27, 28, 30

Dosing		Subjects	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	30
Route of Administration:	oral	**No. of Subjects Completing:**	29**
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	29**
Number of Doses:	N/A	**No. of Dropouts:**	1
Loading Dose:	N/A	**Sex(es) Included:**	Female***
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	67

**One subject (#3) withdrew voluntarily before Period II (Reference) dosing.

***Demographic Table:

No of Subj	Race						Sex		Age Group (Yr.)		Height (cm)		Weight (kg.)	
Total	A[¶]	B[¶]	C[¶]	H[¶]	NA[¶]	OT[¶]	Male	Female	18-40	41-65	Mean	Range	Mean	Range
30	0	1	29	0	0	0	0	30	30	0	166	152.4-180.3	66.3	48.9-152.4

[¶]A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American, OT: Other

Inclusion Criteria Female volunteers 18 to 35 years of age, of childbearing potential, practicing an acceptable method of birth control for the duration of the study judged by clinical investigator(s) as described in the protocol.

Exclusion Criteria Details described in protocol Vol. 1.4, 2780. Volunteers who report taking any systemic prescription medication in the 14 days or taking any estrogen-containing oral contraceptive within 28 days prior to Period I dosing. Volunteers with a history of allergic response to norgestimate, ethinyl estradiol or related drugs.

Confinement: Subjects were housed from the evening before dosing until 24-hour blood draw, and returned for all subsequent blood draws.

Blood Sampling: Samples for ethinyl estradiol and norgestimate were collected separately in EDTA vacutainers and sodium heparin vacutainers, respectively at the following times: Predose and at 0.25, 0.5, 0.75, 1, 1.50, 2, 2.5, 3, 4, 6, 10, 14, 24, 36, 72 and 96 hours postdose (1 x 10 mL each). Samples were centrifuged at 2400 rpm at 4 °C and stored at –22 °C $\pm$ 10 °C pending assay.

Study Results

1) Clinical

Adverse Events: During the study 67 (40 test and 27 ref) adverse events were reported by 22 of the 30 subjects. The adverse events are summarized in the table below:

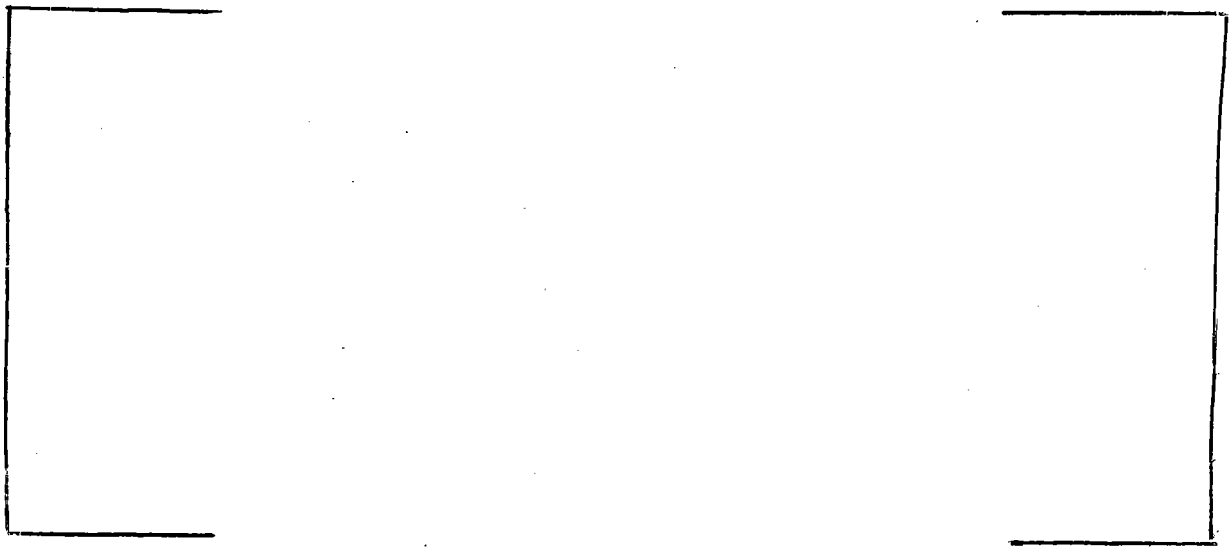
Adverse Events	No of Adv. Events	Test	Ref	Relationship to study drugs
Dizziness	4	3	1	Unrelated
Headache	15	8	7	Probable/Unrelated
Nausea	6	3	3	Possible/Probable/Remote
Vomiting*	6	4	2	Possible/Probable/Remote
Sore Throat	2	1	1	Unrelated
Stomach Cramp/Ache	7	3	4	Possibly
Malaise (Head cold)	5	4	1	Unrelated
Rhinitis	2	2	0	Unrelated/Remote
Chest Cold	1	0	1	Unrelated
Coughing	1	1	0	Unrelated
Queasy	2	2	0	Unrelated
Diarrhea	1	1	0	Remote
Fatigue	1	1	0	Possible
Feels Weak	2	1	1	Possible
Back Pain/Strained Back	2	2	0	Remote/Unrelated
Dyspepsia	1	0	1	Probable
Purpura	3	2	1	Unrelated
Arm/Wrist Pain	2	0	2	Unrelated
Heavy Menstrual Flow	1	1	0	Unrelated
Intermenstrual bleeding	1	0	1	Remote
Vaginal Irritation	1	1	0	Unrelated
Lump on left neck	1	0	1	Unrelated

**All the six episodes of vomiting were experience by Subject #14 at approximately 10.5 and 11 hours in Period I (Ref) and at 9.25, 10.0, 10.5 and 11.75 hours after Period II (Test) dose administrations. None of these episodes were considered serious or required termination of the patient (Vol. 1.4, page 2558).*

Safety Monitoring: Blood pressure and heart rate measures were performed prior to dosing, at 12 and 24 hours after dose administration, and upon completion of the study.

Protocol Deviations: None other than minor sampling deviations.

2) Analytical (Not to be released under FOI)



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BIOEQUIVALENCE REVIEW

Analytical Repeats:

Ethinyl Estradiol: A total of 1044 samples were analyzed. Forty (3.8%) of the samples analyzed were repeated due to analytical reasons (page 2157, Vol. 1.4). Twenty-nine of these repeats were due to LOQ being rejected, 5 each were due to inconsistent internal standard response and incorrect chromatography, and one repeat was done by mistake. The firm has followed SOP No. DH 3.8 for the repeat assays (Vol. 1.4, pp. 2141).

17-Deacetyl Norgestimate: A total of 1039 samples were analyzed. One hundred and sixty-one (15.5%) of the samples analyzed were repeated due to analytical reasons (Vol. 1.2. pp. 1361). One hundred and forty-seven (14.15%) of these repeats were due to samples with calculated values above the highest calibration standard and 14 (1.35%) repeats were due to samples lost in processing. The firm has followed SOP No. AL-G-1506-13 for the repeat assays (Vol. 1.2, pp. 1329).

COMMENTS ON ANALYTICAL METHOD VALIDATIONS:

Observed plasma concentrations for ethinyl estradiol were well within the upper calibration limit of 500 pg/mL.

Several of the observed plasma concentrations for 17-Deacetyl norgestimate exceeded the upper limit of quantitation 2481.6 pg/mL with values in the range of 3000-3900 pg/mL. However, it is noted that the firm has provided validated and acceptable dilution integrity for this analyte – covering a concentration up to 9983.5 pg/mL.

Based on the firm's reported results, analyses for plasma 17-Deacetyl norgestimate and ethinyl estradiol were completed on 12/04/01 and 11/15/01, respectively. Considering the clinical study initiation day on August 08, 2001, the overall storage periods for the plasma 17-Deacetyl norgestimate and ethinyl estradiol, are 116 and 97 days, respectively. The firm has submitted long-term frozen stability study covering a period of 604 days for 17-Deacetyl norgestimate and 61 days only for ethinyl estradiol . Analytical method validation for ethinyl estradiol in the assay of plasma samples obtained in the study is therefore incomplete.

3) Pharmacokinetic and Statistical Analysis:

The firm has submitted plasma concentrations and PK statistical data on Ethinyl Estradiol, 17-Deacetyl Norgestimate, ———— and Norgestimate. It is noted that statistical analyses on ethinyl estradiol and 17-Deacetyl norgestimate only were considered in establishing bioequivalency in this study per protocol (Vol. 1.4, pp. 2774). The data on the other two analytes are provided for supplement purpose only (Vol. 1.2, pp. 0994). Additionally, the firm did not provide computer diskettes containing plasma concentrations and PK data for ———— and norgestimate components. Thus, the reviewer performed statistical analyses on ethinyl estradiol and 17-Deacetyl norgestimate only.

Ethinyl Estradiol: Tables 1-6

17-Deacetyl Norgestimate: Tables 7-11

Table 1. Mean Plasma **Ethinyl Estradiol** Levels (pg/mL) for Test (T) and Reference (R) Products (N=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

TIME Hr	Test	Test SD	Ref	Ref SD	T/R
0	0.00	0.00	0.00	0.00	.
0.25	19.82	19.34	21.66	23.70	0.91
0.5	98.99	61.77	97.73	68.53	1.01
0.75	158.81	70.83	147.52	72.26	1.08
1	180.56	65.09	180.97	82.92	1.00
1.5	185.93	62.30	191.51	61.32	0.97
2	169.03	50.81	179.03	52.38	0.94
2.5	148.22	43.68	161.13	50.11	0.92
3	131.60	36.98	141.14	42.13	0.93
4	104.35	29.61	111.56	33.63	0.94
6	67.94	18.24	74.09	23.13	0.92
10	38.56	10.04	41.35	13.03	0.93
14	28.60	9.26	30.93	9.72	0.92
24	15.22	5.43	16.41	5.76	0.93
36	8.52	3.67	9.75	3.76	0.87
48	10.77	32.65	5.42	2.57	1.99
72	0.66	1.20	0.94	1.44	0.70
96	0.00	0.00	0.00	0.00	.

Table 2. Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287
Arithmetic Means (±SD) of Pharmacokinetic Parameters for **Ethinyl Estradiol** (N = 29)

PK Measures	Test (mean)	Test SD	Ref (mean)	Ref SD
AUCt (pg•hr/mL)	1563.49	456.03	1652.64	520.52
AUCi (pg•hr/mL)	1623.38	460.69	1732.59	518.31
Cmax (pg/mL)	197.86	64.90	204.79	71.68
tmax (hr)	3.07	8.65	1.48	0.49
k_{el} (1/hr)	0.06	0.01	0.05	0.01
t½ (hr)	13.27	3.51	13.98	3.47

Table 3. Summary Statistics for **Ethinyl Estradiol** Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287 Under Fasting Conditions, N = 29

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (pg•hr/mL)	1500.07	1570.37	0.1276	0.96	90.2-101.1
Ln AUCi (pg•hr/mL)	1539.32	1653.62	0.0887	0.93	89.5-96.8
Ln Cmax (pg/mL)	187.36	192.91	0.1443	0.97	91.1-103.6

**Geometric mean values for ln-transformed data reported*

Table 4. **Ethinyl Estradiol**: Test (T) Product/Reference (R) Product Ratios For Individual Subjects (n=29), . Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

OBS	SUB	SEQ	AUCT(T/R)	AUCI(T/R)	CMAX(T/R)	TMAX(T/R)	KE(T/R)	THALF(T/R)
1	1	2	0.87	0.88	1.01	1.00	1.07	0.94
2	2	1	0.96	0.95	0.85	1.00	1.11	0.90
3	4	2	0.92	0.93	0.81	1.33	1.05	0.95

4	5	1	0.99	1.00	0.90	1.33	0.73	1.36
5	6	1	1.11	1.12	1.21	1.00	0.96	1.04
6	7	1	0.91	0.93	0.88	1.00	1.22	0.82
7	8	1	1.09	1.07	1.12	0.50	1.06	0.95
8	9	1	0.87	0.87	0.89	0.50	0.94	1.07
9	10	1	0.90	0.91	1.01	1.00	0.74	1.36
10	11	2	1.02	1.00	0.92	1.00	1.21	0.82
11	12	1	1.08	1.09	0.96	1.50	1.34	0.75
12	13	2	0.76	0.80	0.85	0.75	1.08	0.93
13	14	2	1.03	1.03	0.92	1.33	1.07	0.93
14	15	1	1.07	1.07	1.07	1.00	0.95	1.06
15	16	2	0.95	0.95	0.92	1.50	0.98	1.02
16	17	2	1.09	1.08	1.03	0.50	1.23	0.81
17	18	1	1.14	1.14	1.36	0.60	1.10	0.91
18	19	1	0.85	0.87	1.21	0.67	0.80	1.24
19	20	1	0.98	0.92	1.16	1.33	1.93	0.52
20	21	2	0.74	0.75	0.75	1.50	1.56	0.64
21	22	2	1.85	.	1.49	24.0	.	.
22	23	2	0.83	0.84	1.05	1.00	0.89	1.12
23	24	2	0.81	0.82	0.77	2.50	0.85	1.18
24	25	2	0.83	0.84	1.11	0.75	0.97	1.03
25	26	1	0.91	0.94	0.81	1.00	0.77	1.30
26	27	2	0.77	0.78	0.77	1.50	0.88	1.14
27	28	2	0.84	0.76	0.60	2.00	1.98	0.51
28	29	1	0.86	0.81	0.88	0.75	1.33	0.75
29	30	2	1.13	1.16	1.40	0.75	0.73	1.36

Table 5. **Ethinyl Estradiol**: Ratio of Sponsor (O) /Reviewer (N) Calculated Parameters (N=29), Study #R01-287

OBS	SUB	SEQ	PER	TRT	AUCTO/N	AUCIO/N	CMAXO/N	TMAXO/N
1	1	2	2	1	0.99	0.99	1	1.05
2	2	1	1	1	1.00	1.00	1	1.00
3	4	2	2	1	1.00	1.00	1	1.00
4	5	1	1	1	1.00	1.00	1	1.00
5	6	1	1	1	1.00	1.00	1	1.00
6	7	1	1	1	1.00	1.00	1	1.00
7	8	1	1	1	1.00	1.00	1	1.00
8	9	1	1	1	1.00	1.00	1	1.00
9	10	1	1	1	1.00	1.00	1	1.00
10	11	2	2	1	1.00	1.00	1	1.00
11	12	1	1	1	1.00	1.00	1	1.00
12	13	2	2	1	1.00	1.00	1	1.04
13	14	2	2	1	1.00	1.00	1	1.00
14	15	1	1	1	1.00	1.00	1	1.00
15	16	2	2	1	1.00	1.00	1	1.00
16	17	2	2	1	1.00	1.00	1	1.00
17	18	1	1	1	1.00	1.00	1	1.00
18	19	1	1	1	1.00	1.00	1	1.00
19	20	1	1	1	1.00	1.00	1	1.00
20	21	2	2	1	1.00	1.00	1	1.00
21	22	2	2	1	1.05	.	1	1.02
22	23	2	2	1	0.99	0.99	1	1.00
23	24	2	2	1	1.00	1.00	1	1.00
24	25	2	2	1	1.00	1.00	1	1.00
25	26	1	1	1	1.00	1.00	1	1.00
26	27	2	2	1	1.00	1.00	1	1.00

27	28	2	2	1	1.00	1.00	1	1.00
28	29	1	1	1	1.00	1.00	1	1.00
29	30	2	2	1	1.00	1.00	1	1.00
30	1	2	1	2	0.93	0.97	1	1.00
31	2	1	2	2	1.00	1.00	1	1.00
32	4	2	1	2	1.00	1.00	1	1.00
33	5	1	2	2	1.00	1.00	1	1.00
34	6	1	2	2	1.00	1.00	1	1.00
35	7	1	2	2	1.00	1.00	1	1.00
36	8	1	2	2	1.00	1.00	1	1.00
37	9	1	2	2	1.00	1.00	1	1.00
38	10	1	2	2	1.00	1.00	1	1.00
39	11	2	1	2	1.00	1.00	1	1.00
40	12	1	2	2	1.00	1.00	1	1.00
41	13	2	1	2	1.00	1.00	1	1.00
42	14	2	1	2	1.00	1.00	1	1.00
43	15	1	2	2	1.00	1.00	1	1.00
44	16	2	1	2	1.00	1.00	1	1.00
45	17	2	1	2	1.00	1.00	1	1.00
46	18	1	2	2	1.00	1.00	1	1.00
47	19	1	2	2	1.00	1.00	1	1.00
48	20	1	2	2	1.00	1.00	1	1.00
49	21	2	1	2	1.00	1.00	1	1.00
50	22	2	1	2	1.00	1.00	1	1.00
51	23	2	1	2	1.00	1.00	1	1.00
52	24	2	1	2	1.00	1.00	1	1.00

Table 6. **Ethinyl Estradiol**: AUCT/AUCI Ratio For Individual Subjects (N=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

OBS	SUB	TRT	AUCRATIO
1	1	1	0.94
2	2	1	0.98
3	4	1	0.96
4	5	1	0.98
5	6	1	0.91
6	7	1	0.93
7	8	1	0.95
8	9	1	0.96
9	10	1	0.97
10	11	1	0.95
11	12	1	0.97
12	13	1	0.93
13	14	1	0.96
14	15	1	0.97
15	16	1	0.98
16	17	1	0.96
17	18	1	0.95
18	19	1	0.93
19	20	1	0.95
20	21	1	0.95
21	22	1	.
22	23	1	0.97
23	24	1	0.95
24	25	1	0.97
25	26	1	0.93

26	27	1	0.92
27	28	1	0.95
28	29	1	0.94
29	30	1	0.95
30	1	2	0.96
31	2	2	0.97
32	4	2	0.97
33	5	2	0.98
34	6	2	0.91
35	7	2	0.95
36	8	2	0.94
37	9	2	0.96
38	10	2	0.98
39	11	2	0.93
40	12	2	0.97
41	13	2	0.97
42	14	2	0.96
43	15	2	0.97
44	16	2	0.98
45	17	2	0.94
46	18	2	0.95
47	19	2	0.95
48	20	2	0.89
49	21	2	0.97
50	22	2	0.92
51	23	2	0.98
52	24	2	0.95
53	25	2	0.98
54	26	2	0.96
55	27	2	0.94
56	28	2	0.86
57	29	2	0.88
58	30	2	0.98

Table 7. Mean Plasma **17-Deacetyl Norgestimate** Levels (pg/mL) for Test and Reference Products (N=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

Time Hr	Test	Test SD	Ref	Ref SD	T/R
0	0.00	0.00	0.00	0.00	
0.25	35.37	41.58	157.09	194.51	0.23
0.5	555.49	361.08	1168.87	826.90	0.48
0.75	1512.38	692.90	2079.17	1033.56	0.73
1	2208.69	741.93	2650.67	1141.57	0.83
1.5	2788.31	761.75	2929.41	887.51	0.95
2	2638.14	807.61	2813.79	601.83	0.94
2.5	2342.41	590.37	2383.31	518.83	0.98
3	1959.06	501.07	2007.53	483.34	0.98
4	1465.60	359.93	1535.12	417.66	0.95
6	828.91	203.19	897.25	242.75	0.92
10	532.29	155.12	550.67	146.41	0.97
14	449.56	157.88	463.34	112.26	0.97
24	335.13	89.17	342.37	75.70	0.98
36	224.90	58.05	253.06	50.51	0.89
48	240.91	397.51	184.16	47.41	1.31
72	85.00	28.92	97.46	34.89	0.87
96	45.51	23.58	50.18	23.20	0.91

Table 8. Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287 Arithmetic Means (±SD) of Pharmacokinetic Parameters for **17-Deacetyl Norgestimate** (N = 29)

PK Measures	Test (mean)	Test SD	Ref (mean)	Ref SD
AUCt (pg•hr/mL)	29960.59	8723.29	30931.44	6239.11
AUCi (pg•hr/mL)	31852.82	8842.61	33026.00	6626.20
Cmax (pg/mL)	3017.63	579.32	3174.48	787.29
tmax (hr)	3.31	8.60	1.51	0.43
k_{el} (1/hr)	0.03	0.01	0.03	0.01
t½ (hr)	25.34	6.55	26.14	5.31

Table 9. Summary Statistics for **17-Deacetyl Norgestimate** Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287 Under Fasting Conditions, N = 29

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (pg•hr/mL)	29878.79	30901.66	0.1642	0.96	88.8-102.9
Ln AUCi (pg•hr/mL)	31774.33	32991.83	0.1506	0.95	89.1-102.0
Ln Cmax (pg/mL)	3013.54	3013.54	0.1377	0.96	90.4-102.3

**Geometric mean values for ln-transformed data reported*

Table 10. **17-Deacetyl Norgestimate:** Test (T) Product/Reference (R) Product Ratios For Individual Subjects (n=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

OBS	SUB	SEQ	AUCT(T/R)	AUCI(T/R)	CMAX(T/R)	TMAX(T/R)	KE(T/R)	THALF(T/R)
1	1	2	0.86	0.83	1.04	1.33	1.22	0.82
2	2	1	0.98	1.02	0.89	1.00	0.76	1.32
3	4	2	0.77	0.82	1.09	1.00	0.71	1.40
4	5	1	0.92	0.92	0.79	2.00	0.97	1.03
5	6	1	1.01	0.97	1.23	0.75	1.17	0.86
6	7	1	0.88	0.86	0.79	1.00	1.18	0.85
7	8	1	1.00	0.98	0.96	1.00	1.25	0.80
8	9	1	0.99	1.00	1.24	1.00	0.97	1.03
9	10	1	0.99	0.98	1.05	1.00	1.06	0.94
10	11	2	0.95	0.95	0.92	1.00	0.92	1.08
11	12	1	1.02	1.02	0.87	2.00	1.08	0.92
12	13	2	0.79	0.78	0.92	1.50	1.17	0.86
13	14	2	0.90	0.90	0.81	1.00	1.20	0.83
14	15	1	0.79	0.82	0.97	1.00	0.88	1.13
15	16	2	1.21	1.22	1.12	1.50	0.89	1.13
16	17	2	0.97	0.95	0.82	0.67	1.15	0.87
17	18	1	1.02	1.05	0.93	1.00	0.79	1.26
18	19	1	0.85	0.86	1.37	1.50	1.01	0.99
19	20	1	0.94	0.96	1.29	0.67	0.94	1.06
20	21	2	0.91	0.89	0.61	2.50	1.15	0.87
21	22	2	2.80	2.51	1.09	24.0	3.55	0.28
22	23	2	0.93	0.92	1.11	1.33	1.10	0.91
23	24	2	0.87	0.88	0.95	1.50	0.96	1.04
24	25	2	0.94	0.94	0.76	1.33	1.02	0.98
25	26	1	0.77	0.81	0.65	1.33	0.82	1.21
26	27	2	1.02	1.01	0.87	2.00	1.01	0.99
27	28	2	1.01	1.00	1.10	1.33	1.02	0.98
28	29	1	0.78	0.78	1.04	0.75	0.94	1.07
29	30	2	0.87	0.86	1.06	0.75	1.05	0.95

Table 11. **17-Deacetyl Norgestimate:**: Ratio of Sponsor (O) /Reviewer (N) Calculated Parameters (N=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

OBS	SUB	SEQ	PER	TRT	AUCT O/N	AUCI O/N	CMAX O/N	TMAX O/N
1	1	2	2	1	1	1	1	1.00
2	2	1	1	1	1	1	1	1.00
3	4	2	2	1	1	1	1	1.00
4	5	1	1	1	1	1	1	1.00
5	6	1	1	1	1	1	1	1.00
6	7	1	1	1	1	1	1	1.00
7	8	1	1	1	1	1	1	1.00
8	9	1	1	1	1	1	1	1.00
9	10	1	1	1	1	1	1	1.00
10	11	2	2	1	1	1	1	1.00
11	12	1	1	1	1	1	1	1.00
12	13	2	2	1	1	1	1	1.00
13	14	2	2	1	1	1	1	1.05
14	15	1	1	1	1	1	1	1.00
15	16	2	2	1	1	1	1	1.00
16	17	2	2	1	1	1	1	1.00
17	18	1	1	1	1	1	1	1.00
18	19	1	1	1	1	1	1	1.00
19	20	1	1	1	1	1	1	1.00
20	21	2	2	1	1	1	1	1.00
21	22	2	2	1	1	1	1	1.02
22	23	2	2	1	1	1	1	1.00
23	24	2	2	1	1	1	1	1.00
24	25	2	2	1	1	1	1	1.00
25	26	1	1	1	1	1	1	1.00
26	27	2	2	1	1	1	1	1.00
27	28	2	2	1	1	1	1	1.00
28	29	1	1	1	1	1	1	1.00
29	30	2	2	1	1	1	1	1.00
30	1	2	1	2	1	1	1	1.00
31	2	1	2	2	1	1	1	1.00
32	4	2	1	2	1	1	1	1.00
33	5	1	2	2	1	1	1	1.00
34	6	1	2	2	1	1	1	1.00
35	7	1	2	2	1	1	1	1.00
36	8	1	2	2	1	1	1	1.00
37	9	1	2	2	1	1	1	1.00
38	10	1	2	2	1	1	1	1.00
39	11	2	1	2	1	1	1	1.00
40	12	1	2	2	1	1	1	1.00
41	13	2	1	2	1	1	1	1.00
42	14	2	1	2	1	1	1	1.00
43	15	1	2	2	1	1	1	1.00
44	16	2	1	2	1	1	1	1.00
45	17	2	1	2	1	1	1	1.00
46	18	1	2	2	1	1	1	1.00
47	19	1	2	2	1	1	1	1.00
48	20	1	2	2	1	1	1	1.00
49	21	2	1	2	1	1	1	1.00
50	22	2	1	2	1	1	1	1.00
51	23	2	1	2	1	1	1	1.00
52	24	2	1	2	1	1	1	1.00

53	25	2	1	2	1	1	1	1.00
54	26	1	2	2	1	1	1	1.00
55	27	2	1	2	1	1	1	1.05
56	28	2	1	2	1	1	1	1.00
57	29	1	2	2	1	1	1	1.02
58	30	2	1	2	1	1	1	1.00

Table 5. **17-Deacetyl Norgestimate:** AUCT/AUCI Ratio For Individual Subjects (N=29), Fasting Single-Dose (1x2 tablets) In Vivo Bioequivalence Study #R01-287

OBS	SUB	TRT	AUCRATIO
1	1	1	0.93
2	2	1	0.90
3	4	1	0.90
4	5	1	0.98
5	6	1	0.92
6	7	1	0.96
7	8	1	0.96
8	9	1	0.91
9	10	1	0.98
10	11	1	0.94
11	12	1	0.97
12	13	1	0.93
13	14	1	0.95
14	15	1	0.91
15	16	1	0.94
16	17	1	0.95
17	18	1	0.94
18	19	1	0.94
19	20	1	0.94
20	21	1	0.93
21	22	1	0.98
22	23	1	0.98
23	24	1	0.88
24	25	1	0.98
25	26	1	0.86
26	27	1	0.96
27	28	1	0.96
28	29	1	0.90
29	30	1	0.95
30	1	2	0.90
31	2	2	0.93
32	4	2	0.95
33	5	2	0.98
34	6	2	0.88
35	7	2	0.94
36	8	2	0.95
37	9	2	0.91
38	10	2	0.97
39	11	2	0.95
40	12	2	0.97
41	13	2	0.91
42	14	2	0.94
43	15	2	0.94
44	16	2	0.95
45	17	2	0.93
46	18	2	0.97
47	19	2	0.94
48	20	2	0.97
49	21	2	0.92
50	22	2	0.88
51	23	2	0.97
52	24	2	0.89

53	25	2	0.98
54	26	2	0.91
55	27	2	0.96
56	28	2	0.94
57	29	2	0.90
58	30	2	0.94

Reassays:

For 17D-Norgestimate: No repeat due to any pharmacokinetic anomaly has been reported.

For Ethinyl Estradiol:

Three samples out of 1044 (0.3%) were repeated due to pharmacokinetic anomalies.

For the PK repeat for subject 22, period 2, 48-hour sampling time - the repeat values (—and —pg/mL) confirmed the original value of — pg/mL, and the original value was used.

For the PK repeat for subject 20, period 1, 2-hour time point - average value (2.42 pg/mL) of the three replicates (———— and —pg/mL) was used. The original value at this time-point was — pg/mL. The tmax and Cmax for this subject were 0.75 hr and 176 pg/mL, respectively.

For the PK repeat for subject 20, period 1, 36-hour time point - replicates values of —— ——and — pg/mL did not confirm either each other or the original value (—— pg/mL). Average value of 2.58 pg/mL of the replicates was reported. The tmax and Cmax for this subject were 1.0 hr and 204.0 pg/mL, respectively.

Comments on Repeat Assays: The firm has used repeat assays per protocol. Furthermore, in the reviewer's opinion the repeat values will not have any significant impact on the PK parameters.

Comments: On pharmacokinetic/statistical data:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, t_{max} *and* $t_{1/2}$) and 90% confidence intervals for 17-Deacytl norgestimate and ethinyl estradiol were re-calculated by the reviewer, and were in agreement with the values determined by the firm.
2. The ratios for individual AUCt, AUCi, Cmax and Tmax between the firm's and FDA calculated values were in the range of 0.93-1.05 for both 17-Deacetyl norgestimate and ethinyl estradiol.
3. The mean Tmax values for the Test and Reference Ethinyl Estradiol were 3.07 hr (SD $\pm$ 8.65) and 1.48 hr (SD $\pm$ 0.49), respectively. The reviewer notes that the Test and Ref individual Tmax values were in the range of 0.75 to 2.0 hr and 0.75 to2.03 hr, respectively, except for Subject 22 (Test) that exhibited a Tmax of 49.03 hr (Vol. 1.2, pp. 1014).
4. The mean Tmax values for the Test and Reference 17-Deacetyl norgestimate were 3.31 hr (SD $\pm$ 8.60) and 1.51 hr (SD $\pm$ 0.43) respectively. The Test and Ref individual

Tmax values were in the range of 1.0 to 2.0 hr (**Mode**: 1.5 hr for Test=14 subjects and Ref=17 subjects). However, Subject 22 (Test), exhibited a Tmax of 4.0 hr (Vol. 1.2, pp. 1161).

5. There were no statistically significant period effects for any of these PK measures.
6. The 90% confidence intervals for ln-AUC_t, ln-AUC_i, and ln-C_{max} ratios for 17-Deacetyl norgestimate and ethinyl estradiol are within the acceptable limits of 80-125%.
7. The last sample collection time point (96-hr) in Period I exhibited plasma 17-Deacetyl norgestimate levels in detectable amounts in almost all subjects. The observed mean t1/2 values are 25 and 26 hours respectively, for test and reference products. The washout period of the length of each subject's menstrual cycle appears adequate to ensure that the pre-dose plasma drug concentrations in Period II were below the limit of quantitation for all subjects.
8. The fasting study is incomplete due to deficiency in the analytical method validation of ethinyl estradiol on the long-term frozen stability.

Formulation (Not to be released under FOI)

Ingredient	mg/tablet	
	(0.250 mg/0.035 mg)	Placebo
Norgestimate	0.250	N/A
Ethinyl Estradiol, USP	0.035	N/A
Lactose Monohydrate, NF		
Pregelatinized Starch, NF		
Magnesium Stearate, NF		
FD&C Blue #1 HT		
*		
*		
Total Weight	101.5	101.5

**Removed during the manufacturing process.*

Comments on Formulation: All inactive ingredients used in the test product are within the IIG range for solid oral dosage forms.

Dissolution: Currently there is no USP method for this combination product.

The firm has used the following method:

Medium: 900 mL of deionized water containing 500 PPM Tween® 20*
Apparatus: USP Apparatus 2, 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.*

Dissolution Site: Andrx Pharmaceuticals, Ft. Lauderdale, FL

The dissolution results are summarized in the Tables below:

Norgestimate: Dissolution for Test and Reference Products

Test Products: Norgestimate and Ethinyl Estradiol and Norgestimate Dose strength: 0.035 mg/0.25 mg, Lot # TB-021 Reference Products: Ortho-Cyclen® Tablets Dose strength: 0.035 mg/0.25 mg, Lot # 10H006 Assay methodology: HPLC						
NORGESTIMATE: Results of dissolution testing (% dissolved in minutes)						
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

Ethinyl Estradiol: Dissolution for Test and Reference Products

Test Products: Norgestimate and Ethinyl Estradiol Dose strength: 0.250 mg/0.035 mg, Lot # TB-021 Reference Products: Ortho-Cyclen® Tablets Dose strength: 0.035 mg/0.25 mg, Lot # 10H006						
ETHINYL ESTRADIOL: Results of dissolution testing (% dissolved in minutes)						
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

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. It is noted that more than 85% of each of the active components of the test and reference products is dissolved in 10 minutes. Therefore, the f2 similarity factor was not calculated.

3. The Division has recently recommended the following interim dissolution testing method and specifications for ethinyl estradiol/norgestimate tablet, 0.035/0.25 mg (ANDA 75-804, Barr Laboratories, Submission Date: 02/01/2001; ANDA 75-808, Barr Laboratories, Submission Date: 05/02/2000, also see the Attachment I/I, Consultation with Dr. Nhan Tran, DBE Dissolution Focal Point).

   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C
   Specifications: Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes **[NOT TO BE RELEASED UNDER FOI].**

Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes **[NOT TO BE RELEASED UNDER FOI].**

The OGD Dissolution Database recommends the following:

Apparatus: USP, apparatus 2 (paddle), 75 rpm
Medium: **600 mL** of 0.05% Tween 20, at 37 °C
Specifications: NLT—% (Q) in 30 min for both components **[NOT TO BE RELEASED UNDER FOI].**

The above method is same as recommended for the NDA except that the specification in the NDA method is NLT—% (Q) in 20 minutes for both components (NDA reviews: 19653/S 018, 6/28/1996; 19653/S016, 4/01/1996 and 19653/S020 09/26/1997) **[NOT TO BE RELEASED UNDER FOI].**

4. Firm's dissolution data meet NDA Specifications which are apparently stricter than those suggested by the DBE and/or OGD Dissolution database, however, 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.

Deficiencies:

1. The firm has submitted a long-term frozen stability study for ethinyl estradiol covering a period of 61 days. However, the overall storage period for the plasma ethinyl estradiol samples in the study is 97 days. Thus, analytical method validation for ethinyl estradiol for the assay of plasma samples is deficient, and hence the biostudy is incomplete.
2. The firm's dissolution testing is incomplete.

Recommendations

1. The single-dose fasting study conducted by Andrx Pharmaceuticals on its Ethinyl Estradiol; Norgestimate-28 Tablets 0.035mg/0.25 mg, Lot # TB-021 comparing it to Ortho-Cyclen®-28 tablet, 0.035 mg/0.25 mg, Lot #10H006 is incomplete due to the deficiency in the long-term frozen stability study.

2. The dissolution testing conducted by Andrx on its Ethinyl Estradiol; Norgestimate-28 tablets, 0.035 mg/0.25 mg, Lot #/TB-021 is incomplete. The firm is advised resubmitting 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.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia, Ph.D.
Review Branch I
Division of Bioequivalence

Date: 5/29/2002

RD INITIALED YHUANG
FT INITIALED YHUANG

Date: 5/30/2002

Concur:

Date: 6/6/2002

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

Drug Product: Ethinyl Estradiol; Norgestimate, 0.035 mg/0.25 mg Applicant: Andrx Pharmaceuticals, Inc.

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

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

DRUG PRODUCT: Ethinyl Estradiol; Norgestimate-28 Tablet, 0.035 mg/0.25 mg

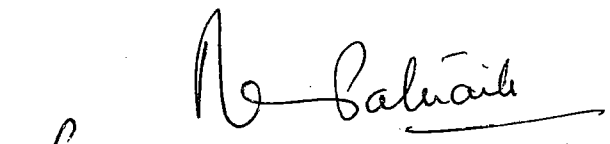
The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have submitted a long-term frozen stability study on ethinyl estradiol covering a period of 61 days only. However, the overall storage period for the plasma ethinyl estradiol samples is 97 days. Therefore, analytical method validation for ethinyl estradiol is deficient, and the biostudy is incomplete.

2. The in vitro dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg is incomplete. You are advised to repeat 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 ^{o}C
   Sampling Times: 10, 20, 30 and 45 minutes.

Sincerely yours,



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

CC: ANDA 76-334
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia 5/29/2002
HFD-652/YC Huang 5/30/2002
HFD-617/ K Scardina 6/10/02
HFD-650/Dale Conner for 6/6/2002

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Printed in Final on 05/29/2002

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

FASTING STUDY (STF) 01 Strength: 0.035 mg/0.25 mg

(Clinical)
(Analytical: for ethinyl estradiol)
(Analytical: for 17-Deacetyl norgestimate)

Outcome: **IC**

Outcome Decisions:
IC - Incomplete

WinBio Comments:

- Fasting bioequivalence study on ethinyl estradiol; norgestimate tablets, 0.035 mg/0.25 mg, is incomplete.
- Dissolution testing on ethinyl estradiol; norgestimate tablets, 0.035 mg/0.25 mg, is incomplete.

Attachment I/I: For ANDA 76-334 Review: Consultation on Dissolution

-----Original Message-----
From: Tran, Nhan L
Sent: Tuesday, May 21, 2002 8:52 AM
To: Chaurasia, Chandra S
Cc: Huang, Yih Chain; Tran, Nhan L; Nerurkar, Shriniwas G
Subject: RE: Dissolution on Ortho Cyclen NDA Method

Chandra:

Thanks for asking the question and it is a good one.

There was an item in the USP/PF Jan/Feb 2002 (pages 79-84) regarding a proposal on the dissolution method and tolerance for this combo drug product, Norgestimate and Ethinyl Estradiol Tablets.

USP Proposal: Apparatus 2 (paddle), 75 rpm
Medium: 600 mL of 0.05% Tween 20 in water, at 37 ^{o}C

The USP proposes to revise the tolerances published previously in the PF 26(5) Sept. - Oct. 2000. The new proposed tolerances are: For 0.180mg/0.035mg tablets and for 0.215mg/0.035mg tablets: NLT (Q) 80%/20 min for both components, and for 0.250mg/0.035mg tablets: NLT (Q) 80%/30 min for both components.

In the response to the USP/PF proposal, we indicated that while we agree with the dissolution method (medium and apparatus), we do not have data to support the proposal on tolerances. Data from our review files (Barr ANDA 75-804, and Duramed ANDA 75-840) indicate that the generic products will have different tolerances as follows: For all tablets strengths: NLT(Q) — %/90 min for norgestimate, and NLT (Q) —%/30 min for ethinyl estradiol.
As you can see from your search, the USP/PF method/specification was originated from the NDA submission, but we cannot apply to the generic firm since they just cannot meet the specifications. Therefore, when we reviewed the data, we came up with the specifications as you have seen in Barr and Duramed applications.

For your submission, I would like to suggest the following:
For all tablets strengths:
1. Review the data to see that if it meets the NDA tolerances, you can suggest the NDA tolerances to the firm, since if it meets the NDA tolerances, it will definitely meet the DBE suggested tolerances.
2. If it cannot meet the NDA tolerances, use the DBE tolerances: NLT(Q) — %/90 min for norgestimate, and NLT (Q) — %/30 min for ethinyl estradiol.
3. If every thing fails, we have to look at the data to see what tolerances we can come up with. It all depends on the data the firm submitted to you.

I hope this will help. Please discuss further if you wish.

Ethinyl Estradiol and Norgestimate Tablet-28
0.035 mg/0.25 mg
ANDA 76-334
Reviewer: Chandra S. Chaurasia
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Andrx Pharmaceuticals, Inc.
Lauderdale, FL 33314
Submission Date: June 27, 2002

Review of an Amendment (Analytical and Dissolution Data)

OBJECTIVE

Review of Andrx Pharmaceuticals' amendment responding to the Agency's letter dated June 11, 2002.

CONTENTS OF SUBMISSION

1. Long-term frozen stability data
2. Dissolution data

REFERENCE LISTED DRUG

Ortho Cyclen -21, manufactured by RW Johnson, Strength: 0.035 mg; 0.25 mg

BACKGROUND

Andrx Pharmaceuticals previously submitted single-dose bioequivalence study under fasting condition comparing its Ethinyl Estradiol; Norgestimate-28 Tablets 0.035mg/0.25 mg, Lot # TB-021 to Ortho-Cyclen®-28 tablet, 0.035 mg/0.25 mg, Lot #10H006 manufactured by RW Johnson; Submission Date: December 27, 2001; Review Date: June 06, 2002. The biostudy was found incomplete due to the deficiency in the long-term frozen stability study on ethinyl estradiol. In the original application, the firm has submitted a long-term frozen stability study for this analyte covering a period of 61 days only. Whereas, the overall storage period for the plasma ethinyl estradiol samples was 97 days.

In addition, the dissolution testing method used by the firm in the original application was found deficient. The firm was advised to use the following 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.

In the current submission, the firm has responded to the above deficiencies.

REVIEW OF THE FIRM'S RESPONSE

Deficiency 1: *You have submitted a long-term frozen stability study on ethinyl estradiol covering a period of 61 days only. However, the overall storage period for the plasma*

ethinyl estradiol samples is 97 days. Therefore, analytical method validation for ethinyl estradiol is deficient, and the biostudy is incomplete.

Firm's Response:

The firm has provided additional long-term frozen stability data for ethinyl estradiol in plasma stored at –20 °C for 71 weeks for QC samples (15 pg/mL, 75 pg/mL and 375 pg/mL) and for 45 weeks for QC sample 3.0 pg/mL. Six sets of controls at each of these concentrations were stored at –20 °C for the specified periods of time (Vol. 2.1, pp. 23-24) and re-analyzed using ——— method as discussed in the original ANDA submission. The results show that the percent changes for ethinyl estradiol in human plasma over the specified storage periods were in the range of -1.0% to 4.0% (with a CV in the range of 2.5% to 12%).

Comments on Analytical Methodology:

The analytical method validation for ethinyl estradiol is acceptable.

Deficiency 2: *The in vitro dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg is incomplete. You are advised to repeat 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, 0.035 mg/0.25 mg using the Agency's recommended method. The dissolution results are given in the table below:

Dissolution for Test and Reference Products

Test Products: Norgestimate and Ethinyl Estradiol Dose strength: 0.035 mg/0.25 mg, Lot # TB-021 Reference Products: Ortho-Cyclen® Tablets Dose strength: 0.035 mg/0.25 mg, Lot # 10H006						
NORGESTIMATE: Results of dissolution testing (% dissolved in minutes)						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	90		4.1	94		3.8
20	92		2.6	96		2.3
30	92		3.0	96		1.9
45	92		2.4	98		1.3
ETHINYL ESTRADIOL: Results of dissolution testing (% dissolved in minutes)						
Sampling time (min)	Test product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
10	92		2.2	100		0.8
20	93		1.9	101		0.8
30	93		1.8	101		1.0
45	93		2.1	100		1.0

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. It is noted that ≥ 90% of each of the active components of the test and reference products is dissolved in 10 minutes. Therefore, the f2 similarity factor was not calculated.

3. As mentioned in the original review for this product dated June 06, 2002, the OGD Dissolution Database recommends the following:

   Apparatus: USP, apparatus 2 (paddle), 75 rpm
   Medium: **600 mL** of 0.05% Tween 20, at 37 °C
   Specifications: NLT —% (Q) in 30 min for both components **[NOT TO BE RELEASED UNDER FOI].**

   The above method is same as recommended for the NDA except that the specification in the NDA method is NLT —% (Q) in 20 minutes for both components (NDA reviews: 19653/S 018, 6/28/1996; 19653/S016, 4/01/1996 and 19653/S020 09/26/1997) **[NOT TO BE RELEASED UNDER FOI].**

4. In consultation with Dr. Nhan Tran, OGD dissolution focal point, this reviewer recommends the following interim specification for the test product consistent with that in the NDA recommendation (please see Attachment I/I):

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

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

RECOMMENDATIONS

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

2. The firm has conducted an acceptable dissolution testing on its Ethinyl Estradiol; Norgestimate-28 Tablets 0.035mg/0.25 mg, Lot # TB-021.

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. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

Chandra S. Chaurasia, Ph.D.
Review Branch I
Division of Bioequivalence

Date: 7/25/2002

RD INITIALED YHUANG
FT INITIALED YHUANG

Date: 7/29/2002

Concur:

Date: 9/16/02

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

Drug Product: Ethinyl Estradiol; Norgestimate, 0.035 mg/0.25 mg
Applicant: Andrx Pharmaceuticals, Inc.
V:\firmsam\Andrx\ltrs&rev\76334A0602.doc

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

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

DRUG PRODUCT: Ethinyl Estradiol; Norgestimate-28 Tablet, 0.035 mg/0.25 mg

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

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

CC: ANDA 76-334
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia 7/25/2002
HFD-652/YC Huang 7/29/2002
HFD-617/ K Scardina 8/24/02
HFD-650/Dale Conner 9/16/02

V:\firmsam\Andrx\ltrs&rev\76334A0602.doc

Printed in Final on 07/25/2002

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

Submission Dates: **06/27/2002**

Study Amendment (STA) 01C

Strength: 0.035 mg/0.25 mg

Outcome: **AC**

Outcome Decisions:

AC - Acceptable

WinBio Comments:

- Fasting bioequivalence study on ethinyl estradiol; norgestimate tablets, 0.035 mg/0.25 mg, is acceptable.
- Dissolution testing on ethinyl estradiol; norgestimate tablets, 0.035 mg/0.25 mg, is acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-334 **SPONSOR: Andrx Pharmaceuticals, Inc.**

DRUG AND DOSAGE FORM: Ethinyl Estradiol; Norgestimate Tablet

STRENGTH (S): 0.035 mg/0.25 mg

TYPES OF STUDIES: Fasting Bioequivalence Study

CLINICAL STUDY SITE (S): _____
ANALYTICAL SITE (S): _____

STUDY SUMMARY: Bioequivalence study on Ethinyl Estradiol; Norgestimate Tablet, 0.035 mg/0.25 mg is acceptable.

Dissolution testing on Ethinyl Estradiol; Norgestimate Tablet, 0.035 mg/0.25 mg is acceptable.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. **BRANCH : I**

INITIAL : CS Chaurasia **DATE :** 7/25/2002

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. **BRANCH : I**

INITIAL : YH **DATE :** 7/29/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ **DATE :** 9/16/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

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. M 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
V:\FIRMSAM\ANDRX\TELECONS\76334.76335.tc.121003.doc

Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-334

CORRESPONDENCE

Andrx
PHARMACEUTICALS, INC.

2/26/02 Filing
NDA for
505(b)(2)
J. 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

RE: Norgestimate and Ethinyl Estradiol Tablets, 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, 0.250 mg/0.035 mg. The reference-listed drug is RW Johnson's Ortho-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 **7** volumes. The review copy is divided in two sections. The Chemistry Section (red) copy contains **3** volumes and the Bioequivalence Section (orange) copy contains **5** volumes. 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 correspondance should be addressed to Mr. William Stahovec, Associate Director of Regulatory Affairs, phone number (954) 585-1846.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 3 1 2001

Sincerely,

Diane Servello
Sr. Director of Regulatory Affairs

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

ANDA 76-334

FEB 28 2002

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Ft. Lauderdale, FL 33314

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, 0.25 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,

Harvey A. Greenberg for

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

ANDA 76-334
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 H Mealy 2/27/2002 date
HFD-615/SMiddleton, CSO H Mealy 2/27/2002 date
Word File
V:\FIRMSAM\ANDRX\LTRS&REV\76334.ACK
F/T EEH 02/27/02

ANDA Acknowledgment Letter!

Ok Sandy corrected in typing only

Andrx
PHARMACEUTICALS, INC.

3/14/02 MA J. 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 76-334; Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg

Ms. Saundra Middleton:

As per your request, you will find enclosed originals of a signed Field Copy Certification, Debarment Certification Statement and Environmental Impact Statement.

Also enclosed, as per your request, is 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 14 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

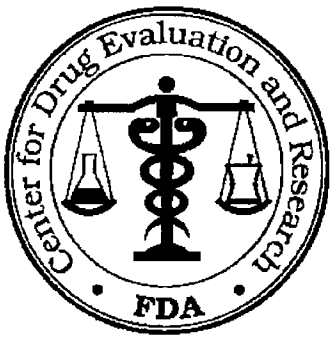
1 Copy

BIOEQUIVALENCY AMENDMENT

ANDA 76-334

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)

JUN 11 2002



TO: APPLICANT: Andrx Pharmaceuticals, Inc. TEL: 954-585-1665

ATTN: Diane Servello FAX: 954-358-6350

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Ms. Servello:

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 Ethinyl Estradiol and Norgestimate Tablets - 28, 0.035 mg/0.25 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___ pages. 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.

SPECIAL INSTRUCTIONS:

JUN 11 2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

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

DRUG PRODUCT: Ethinyl Estradiol; Norgestimate-28 Tablet, 0.035 mg/0.25 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. You have submitted a long-term frozen stability study on ethinyl estradiol covering a period of 61 days only. However, the overall storage period for the plasma ethinyl estradiol samples is 97 days. Therefore, analytical method validation for ethinyl estradiol is deficient, and the biostudy is incomplete.

2. The in vitro dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg is incomplete. You are advised to repeat 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 ^{o}C
   Sampling Times: 10, 20, 30 and 45 minutes.

Sincerely yours,

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

Andrx™
PHARMACEUTICALS, INC.

BIOEQUIVALENCY AMENDMENT

June 27, 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

NDA
ORIG AMENDMENT

RE: ANDA 76-334
Ethinyl Estradiol and Norgestimate Tablets - 28, 0.035 mg/0.25 mg

This letter is in response to your facsimile of June 11, 2002 (copy attached) regarding Andrx's ANDA 76-334, Ethinyl Estradiol and Norgestimate Tablets - 28, 0.035mg/0.25 mg. In accordance with 21 CFR 314.96, Andrx Pharmaceuticals, Inc. is submitting an amendment to this ANDA that provides a complete response to all the deficiencies listed in the correspondence.

Bioequivalence Deficiencies:

Comment

1. You have submitted a long-term frozen stability on ethinyl estradiol covering a period of 61 days only. However, the overall storage period for the plasma ethinyl estradiol samples is 97 days. Therefore, analytical method validation for ethinyl estradiol is deficient, and the biostudy is incomplete.

Response

A revised report, for the Validation of a ——— Method for the Quantitation of Ethinyl Estradiol in EDTA Plasma, demonstrates long-term frozen stability on ethinyl estradiol for a period of 45 weeks at -20°C. A copy of this report is provided in Exhibit 1.

Please note that the validation method used at the ——— at the ——— site is identical to the method used and re-validated at the ——— site in ———. A letter from ———, stating the above is also included in Exhibit 1.

Comment

2. The in vitro dissolution testing conducted on your Ethinyl Estradiol/Norgestimate tablets, 0.035 mg/0.25 mg is incomplete. You are advised to repeat 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.

RECEIVED
JUN 2 8 2002
OGD / CDER

Response

The dissolution profiles were repeated under the following test conditions:

Apparatus:	2 (Paddle)
Medium:	0.05% Tween 20
Volume:	600 ml
Speed:	75 rpm
Temperature:	37.0°C ± 0.5°C

Tables of the data from the dissolution profiles are provided in Exhibit 2.

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,

Diane Servello
Senior Director of Regulatory Affairs

Andrx™
PHARMACEUTICALS, INC.

ANDA 76-334
Norgestimate/Ethinyl Estradiol Tablets, 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: 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

Andrx™
PHARMACEUTICALS, INC.

July 23, 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

NEW CORRESP
NC

RE: ANDA 76-334
Ethinyl Estradiol and Norgestimate Tablets - 28, 0.035 mg/0.25 mg

Dear Ms. Kim:

As per your request, we are providing a clarification of the Central File Number for the manufacturing facility of Ethinyl Estradiol and Norgestimate Tablets – 28, 0.035 mg/0.25 mg.

The Central File Number (CFN) 1058844 submitted in the application applies to Andrx Pharmaceuticals Inc. located at 4955 Orange Drive, Ft. Lauderdale, FL 33314. Mr. Martin Katz with the Orlando District Office was contacted and he was able to confirm this information.

CFN number 1065943 belonged to Aspire Pharmaceuticals, a subsidiary of Andrx Corporation, located on the same campus as Andrx Pharmaceuticals. Aspire Pharmaceuticals merged with Andrx Pharmaceuticals on December 10, 2001. A letter and FDA forms 2656 "Registration of Drug Establishment/Labeler Code Assignment" were mailed to the agency on December 10, 2001 to retire Aspire Pharmaceuticals CFN number 1065943 and to renew Andrx Pharmaceutical CFN number 1058844. Therefore, registration number 1058844 covers 4955 Orange Drive and 4011 S.W. 47th Avenue, as well as other buildings within the campus. A copy of the letter and applications are attached as supporting documentation.

If there are any questions regarding this information, please direct them to William Stahovec at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

Diane Servello
Senior Director of Regulatory Affairs

RECEIVED
JUL 24 2002
OGD / CDER

MINOR AMENDMENT

ANDA 76-334

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, 0.25 mg/0.035 mg (28 day).

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 comments provided. Labeling and Bioequivalency comments will be provided under a separate cover.

SKM
7/23/02

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

7/23/2002 FDA FAX

9. [redacted]

10. [redacted]

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

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Your bioequivalence information (including dissolution data), submitted in the June 27, 2002 Amendment, are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

3. Please note that methods validation will be scheduled after testing issues in this letter are resolved.

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

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,

Paul S Schwoffle

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

Andrx™
PHARMACEUTICALS, INC.

January 6, 2003

NEW CORRESP
NC

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

Re: ANDA 76-334; Norgestimate and/ /Ethinyl Estradiol Tablets, 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

Andrx
PHARMACEUTICALS
L.L.C.

NEW CORRESP
NC

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

Re: ANDA 76-334; Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg

Dear Mr. Buehler:

We refer to a letter dated January 6, 2003 from Andrx Pharmaceuticals, Inc. notifying the agency of a change in ownership of the abbreviated new drug application ("ANDA") listed above. 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, L.L.C. certifies the following:

1. A commitment is made to abide by the agreements, promises and conditions contained in this ANDA
2. A complete copy of the ANDA is in the possession of Andrx Pharmaceuticals, L.L.C.
3. A signed application form is attached

Please continue to address all correspondence regarding this ANDA to the above address.

Please do not hesitate to contact me at (954) 585-1751 if you require any additional information.

Sincerely,

Scott Lodin,
Executive Vice President and General Counsel

RECEIVED
JAN 0 9 2003
OGD / CDER

76-324 (2.1)

ANDA (See Attachment)

Andrx Pharmaceuticals, L.L.C.
Attention: William Stahovec
4955 Orange Avenue
Ft. Lauderdale, FL 33314

MAR 17 2

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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3/17/03 FDA LETTER (ATTACHMENT)

Andrx
PHARMACEUTICALS
LLC

76-
ANDA ~~#75~~-334
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

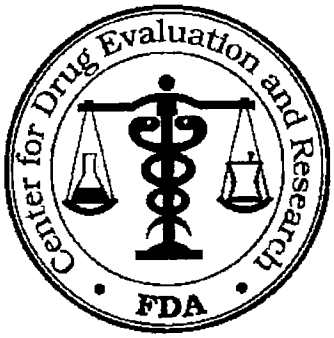
cc: Debbie Catterson (Desk Copy Room N140)

MINOR AMENDMENT

ANDA 76-334

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, 0.250 mg/0.035 mg (28 day regimen).

Reference is also made to your amendment(s) dated: November 22, 2002.

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.

6/30/03

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JULY 1, 2003 FDA FAX

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

1. Please provide updated stability data using the updated new impurity specifications.

2. 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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

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

DRUG PRODUCT: Ethinyl Estradiol; Norgestimate-28 Tablet, 0.035 mg/0.25 mg

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 76-334
Norgestimate and Ethinyl Estradiol Tablets, 0.250 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 76-334, Norgestimate and Ethinyl Estradiol Tablets, 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. [redacted]

Response

[redacted]

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ANDRX 8/11/2003 LETTER

MINOR AMENDMENT

ANDA 76-334

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, 0.250 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,

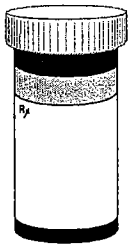
DSGI'M

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

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): 4 **Date:** November 3, 2003

Comments:

Dear Ms. Rance,

Attached is the labeling review of your submission dated May 1, 2003 for ANDA 76-334 for Norgestimate (0.25 mg) and Ethinyl Estradiol (0.035 mg) Tablets.

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: 76-334

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

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

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

Proprietary Name: Previfem™ Tablets

Labeling Deficiencies:

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

   Satisfactory in final print.

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

   Refer to the attached mocked-up copy of your labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.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 labeling.

_2_ pages of draft labeling have been removed from this portion of the document.

11/3/03 FDA FAX

Andrx
PHARMACEUTICALS
LLC

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 76-334
Norgestimate and Ethinyl Estradiol Tablets, 0.250 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 76-334, Norgestimate and Ethinyl Estradiol Tablets, 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. [redacted]

Response

[redacted]

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ANDRX 11/12/03 LETTER

Andrx
PHARMACEUTICALS
LLC

December 9, 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

Attn: Ms. Sara Kim

RE: ANDA 76-334
Norgestimate and Ethinyl Estradiol Tablets, 0.250 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 76-334, Norgestimate and Ethinyl Estradiol Tablets, 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. These have been in the laboratory for 10 months. In addition, there are packaged tablets 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.

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
PHARMACEUTICALS
LLC

TELEPHONE AMENDMENT

December 10, 2003

ORIG AMENDMENT
N/ATM

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

Gentlemen:

This letter is in response to our teleconference of December 5, 2003 regarding Andrx's ANDA 76-334, Norgestimate and Ethinyl Estradiol Tablets, 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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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