DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Kristina Spranger
Manager, Worldwide Regulatory Strategy
Pfizer Inc. 235 East 42nd Street
New York, New York 10017

Re: NDA # 20-130 Estrostep (norethindrone acetate and ethinyl estradiol) Tablets
MACMIS # 9920

Dear Ms. Spranger:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a professional journal advertisement (ID EX053A01) for Estrostep (norethindrone acetate and ethinyl estradiol) Tablets that is misleading and in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Specifically, this journal advertisement claims that there are "new findings" that "show no significant weight gain associated with Estrostep." The claim is misleading because it is not supported by adequate and well-controlled clinical trials. Furthermore, the histogram depicted in the journal advertisement implies that the two-pound difference between Estrostep and placebo is a benefit. However, this difference is not clinically significant.

The journal advertisement cites data from two multi-center 6-month studies to support the claim that Estrostep showed no significant weight gain. These studies are inadequate to support this claim because weight gain or loss was not a prospectively defined endpoint. Instead, it was determined through a post-hoc analysis of the risk assessments from these studies. Thus, DDMAC has concluded that claims that state or imply that weight gain is not a concern with Estrostep are not supported.

To address these objections, DDMAC recommends that Pfizer do the following:

1. Immediately discontinue the use of this journal advertisement and any other promotional material and practices with the same or similar messages, including the tagline "weighs in right for OC users."

2. Respond to this letter by April 30, 2001. Your response should include a statement of your intent to comply with the above, a list of all promotional materials with the same or similar issues, and your methods for discontinuing these promotional materials.

If you have any questions or comments, please contact Dr. Lisa L. Stockbridge by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and

Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 9920 in addition to the NDA number.

Sincerely,

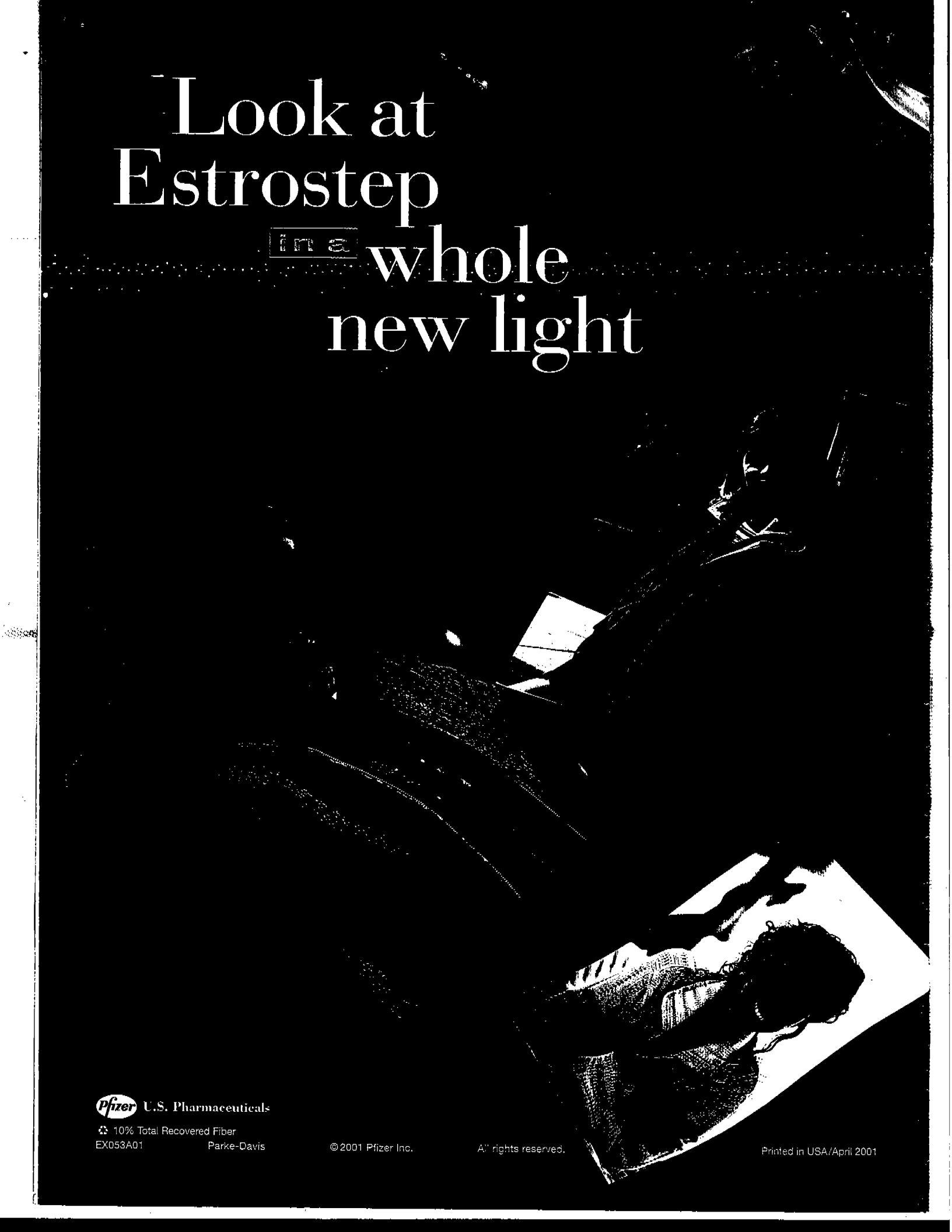
{See appended electronic signature page}

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications

/s/

Lisa Stockbridge
4/16/01 01:33:42 PM

Look at Estrostep in a whole new light



Pfizer U.S. Pharmaceuticals

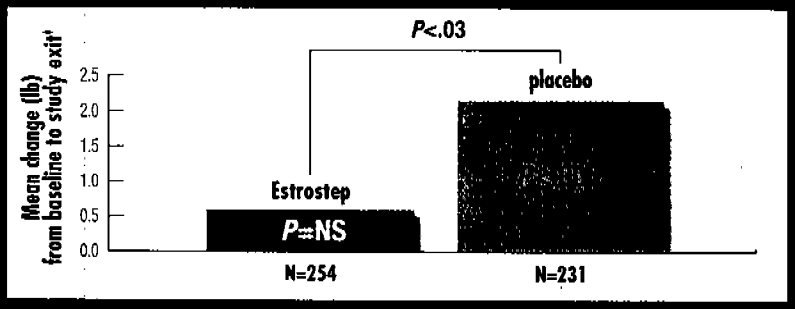
♻ 10% Total Recovered Fiber

EX053A01 Parke-Davis

Printed in USA/April 2001

In oral contraception: New findings show no significant weight gain associated with Estrostep

Combined results from a post-study analysis of weight data from two placebo-controlled trials[1*†]



*Randomized, double-blind, multicenter, 6-month studies in subjects 14–49 years of age (N=693). Body weight and BMI were collected at baseline and study exit. Mean age was 24, with 42% of subjects <22 years of age.

†Results of a combined analysis. N=all randomized subjects who had weight recorded at baseline and study exit; 19 pregnant patients (12 placebo, 1 Estrostep) were removed from the analysis.

‡Mean change=mean of the individual changes from baseline to study exit.

Oral contraceptives are not appropriate for all patients, and serious as well as minor side effects have been reported with the use of all OCs. OCs do not protect against HIV infection (AIDS) and other sexually transmitted diseases. **Cigarette smoking increases the risk of serious cardiovascular side effects, especially in women over the age of 35. Women who use OCs should be strongly advised not to smoke.**

In active-controlled trials, changes in weight (gain or loss) were associated with all OCs.

Please see brief summary of prescribing information, including boxed warning, on next page.

Reference: 1. Data on file. Pfizer Inc., New York, NY.

Estrostep®

norethindrone acetate and ethinyl estradiol tablets—Estrophasic™ Regimen

Weighs in right for OC users

Estrostep®

norethindrone acetate and ethinyl estradiol tablets, USP

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

Before prescribing, please see full prescribing information. A Brief Summary follows:

INDICATIONS AND USAGE: Estrostep is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OCs) as a method of contraception.

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 OCs 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 OCs 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 OCs with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the OCs 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 OC 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 OC users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. 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 OC 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 OC users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with OC 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. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use OCs. OCs may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol, and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. OCs 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. OCs must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism: An increased risk of thromboembolic and thrombotic disease associated with the use of OCs 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. 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. The risk of thromboembolic disease due to OCs is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of OCs. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, OCs should be discontinued at least 4 weeks prior to and for 2 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, OCs should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular disease: OCs 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, while smoking interacted to increase the risk for hemorrhagic strokes. 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. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used OCs, 2.6 for smokers who did not use OCs, 7.6 for smokers who used OCs, 1.8 for normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from OCs: A positive association has been observed between the amount of estrogen and progestogen in OCs and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. 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 OC depends on a balance achieved between doses of estrogen and progestin and the nature of the progestin used in the contraceptives. The amount and activity of both hormones should be considered in the choice of an OC. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular OC, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with the needs of the individual patient. New acceptors of OC agents should be started on preparations containing the lowest dose of estrogen which produces satisfactory results for the patient.

e. Persistence of risk of vascular disease: There are two studies which have shown persistence of risk of vascular disease for ever users of OCs. In a study in the United States, the risk of developing myocardial infarction after discontinuing OCs persists for at least 9 years for women 40-49 years who had used OCs for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of OCs, although excess risk was very small. However, both studies were performed with OC formulations containing 50 mcg or higher of estrogen.

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. 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 OC 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 a possible increase in risk of mortality with age for OC users is based on data gathered in the 1970's but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of OC use to women who do not have the various risk factors listed in this labeling. Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of OCs may now be less than previously observed (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985;66:1-4; and Porter JB, Hershel J, Walker AM. Mortality among oral contraceptive users. Obstet Gynecol 1987;70:29-32), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with OC use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are 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. Therefore, the Committee recommended that the benefits of OC use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take OCs, should take the lowest possible dose formulation that is effective.

3. Carcinoma of the Reproductive Organs: Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using OCs. Most of the studies on breast cancer and OC use report that the use of OCs is not associated with an increase in the risk of developing breast cancer. Some studies have reported an increased risk of developing breast cancer in certain subgroups of OC users, but the findings reported in these studies are not consistent. Some studies suggest that OC use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between OC use and breast and cervical cancers, a cause and effect relationship has not been established.

4. Hepatic Neoplasia: Benign hepatic adenomas are associated with OC 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 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) OC users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in OC users approaches less than one per million users.

5. Ocular Lesions: There have been clinical case reports of retinal thrombosis associated with the use of OCs. OCs 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. OC Use Before and During Early Pregnancy: Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used OCs prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of OCs to induce withdrawal bleeding should not be used as a test for pregnancy. OCs 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 OC 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. OC use should be discontinued if pregnancy is confirmed.

7. Gallbladder Disease: Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of OCs and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among OC users may be minimal. The recent findings of minimal risk may be related to the use of OC formulations containing lower hormonal doses of estrogens and progestogens.

8. Carbohydrate and Lipid Metabolic Effects: OCs have been shown to cause glucose intolerance in a significant percentage of users. OCs containing greater than 75 mcg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, OCs appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking OCs. 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 OC users.

9. Elevated Blood Pressure: An increase in blood pressure has been reported in women taking OCs and this increase is more likely in older OC users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens. Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use OCs, they should be monitored closely, and if significant elevation of blood pressure occurs, OCs should be discontinued. For most women, elevated blood pressure will return to normal after stopping OCs, and there is no difference in the occurrence of hypertension among ever and never users.

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

11. Bleeding Irregularities: Breakthrough bleeding and spotting are sometimes encountered in patients on OCs, especially during the first three months of use. Nonhormonal causes should be considered, and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of prolonged 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.

PRECAUTIONS:

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

2. Physical Examination and Follow-Up: It is good medical practice for all women to have annual history and physical examinations, including women using OCs. The physical examination, however, may be deferred until after initiation of OCs 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.

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

4. 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.

5. Fluid Retention: OCs 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.

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

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

8. Drug Interactions: Effects of Other Drugs on Oral Contraceptives

Rifampin: Metabolism of both norethindrone and ethinyl estradiol is increased by rifampin. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or norethindrone, which could result in a reduction in contraceptive effectiveness.

Troglitazone: Administration of troglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in a reduction of contraceptive effectiveness.

Antibiotics: Pregnancy while taking oral contraceptives has been reported when the oral contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

Other: Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding has been suggested with phenylbutazone.

Effects of Oral Contraceptives on Other Drugs

Oral contraceptive combinations containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance in temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

9. Interactions with Laboratory Tests: Certain endocrine and liver function tests and blood components may be affected by OCs:

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), T_4 by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

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

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

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

10. Carcinogenesis: See **WARNINGS** section.

11. Pregnancy: Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

12. Nursing Mothers: Small amounts of OC 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, OCs 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 OCs but to use other forms of contraception until she has completely weaned her child.

13. Pediatric Use: Safety and efficacy of Estrostep 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.

INFORMATION FOR THE PATIENT: See patient labeling in full prescribing information.

ADVERSE REACTIONS: An increased risk of the following serious adverse reactions has been associated with the use of OCs (see **WARNINGS** section): thrombophlebitis; cerebral hemorrhage; gallbladder disease; arterial thromboembolism; cerebral thrombosis; hepatic adenomas or benign liver tumors; pulmonary embolism; hypertension; myocardial infarction. There is evidence of an association between the following conditions and the use of OCs, although additional confirmatory studies are needed: mesenteric thrombosis; retinal thrombosis. The following adverse reactions have been reported in patients receiving OCs 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 OCs and the association has been neither confirmed nor refuted: pre-menstrual syndrome; hirsutism; impaired renal function; cataracts; loss of scalp hair; hemolytic uremic syndrome; changes in appetite; erythema multiforme; cystitis-like syndrome; erythema nodosum; Budd-Chiari syndrome; headache; hemorrhagic eruption; acne; nervousness; vaginitis; changes in libido; dizziness; porphyria; colitis.

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

HOW SUPPLIED: Estrostep 21 is available in dispensers each containing 21 white tablets. The first five triangle tablets each contain 1 mg of norethindrone acetate and 20 mcg of ethinyl estradiol; the next seven square tablets each contain 1 mg of norethindrone acetate and 30 mcg of ethinyl estradiol; the last nine round tablets each contain 1 mg of norethindrone acetate and 35 mcg of ethinyl estradiol. Available in boxes of five dispensers. Estrostep Fe is available in dispensers each containing 21 white tablets. The first five triangle tablets each contain 1 mg of norethindrone acetate and 20 mcg of ethinyl estradiol; the next seven square tablets each contain 1 mg of norethindrone acetate and 30 mcg of ethinyl estradiol; the next nine round tablets each contain 1 mg of norethindrone acetate and 35 mcg of ethinyl estradiol; and the last seven (brown) tablets each contain 75 mg ferrous fumarate. Available in boxes of five dispensers.

Storage—Do not store above 25° C (77° F). Protect from light. Store tablets inside pouch when not in use.

R_x only

Pfizer **U.S. Pharmaceuticals**

0928G254
Revised November 1999