

208398-1

Levonorgestrel and Ethinyl Estradiol Tablets USP Rx only



208398-1

Revised: March 2012

3 16

FO

FO

FO

FO

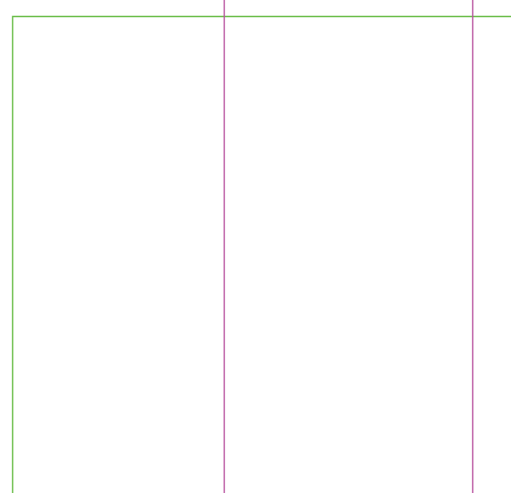
FO

FO

FO

FO

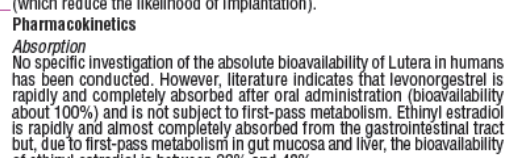
3 16



Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DESCRIPTION Each active, white tablet (21) contains 0.1 mg of levonorgestrel, (d)-13β-ethyl-17α-ethynyl-17β-hydroxy-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3,17β-diol. The inactive ingredients present are croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone.

Each inactive, peach tablet (7) contains the following inactive ingredients: FD&C Yellow #6, lactose anhydrous, magnesium stearate, and microcrystalline cellulose.



CLINICAL PHARMACOLOGY Mode of Action 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 reduces the likelihood of implantation).

Pharmacokinetics Absorption No specific investigation of the absolute bioavailability of Lufeta in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed after oral administration but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

After a single dose of Lufeta to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, taken after day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively (Figure 1). Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are non-linear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Following a single dose, maximum serum concentrations of ethinyl estradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state, taken after day 19 onwards, maximum concentrations of ethinyl estradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinyl estradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinyl estradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21 (FIGURE 1).

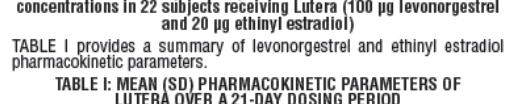


FIGURE 1: Mean (SD) levonorgestrel and ethinyl estradiol serum concentrations in 22 subjects receiving Lufeta (100 µg levonorgestrel and 20 µg ethinyl estradiol)

TABLE I provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters in steady state.

TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF LUFETA OVER A 21-DAY DOSING PERIOD. Columns include Day, Cmax, Tmax, AUC, Cmin, Vd/F, and SHBG.

TABLE II: MEAN (SD) PHARMACOKINETIC PARAMETERS OF UNBOUND LEVONORGESTREL AND ETHINYL ESTRADIOL. Columns include Day, Cmax, Tmax, AUC, Cmin, Vd/F, and SHBG.

TABLE III: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEFECTS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE YEARS BY FERTILITY CONTROL METHOD AND ACCORDING TO AGE.

TABLE III: Annual number of birth-related or method-related defects associated with control of fertility per 100,000 nonsterile years by fertility control method and according to age.

Adapted from H.W. Ory, Family Planning Perspectives, 1957-63, 1983.

3. Carcinoma of the Reproductive Organs and Breasts Reproductive and breast cancer are associated with the use of oral contraceptives and the incidence of breast and cervical cancer.

The risk of having breast cancer diagnosed may be slightly increased in current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after combination oral contraceptive discontinuation and by 10 years after cessation the relative risk disappears. However, there continues to be a controversy about the duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have reported a small increase in risk for women who first use combination oral contraceptives at a younger age. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history. However, there continues to be a 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 combination oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. Hepatic Neoplasia Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of these 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. 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) oral-contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision, or other symptoms of retinal vascular disease, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral-Contraceptive Use and Pregnancy Extensive epidemiological studies have revealed no increased risk of birth defects in infants born to women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in relation to cleft lip and palate, when oral-contraceptive use has been discontinued prior to pregnancy. However, there is a small increase in the risk of miscarriage and stillbirth in infants born to women who have used oral contraceptives during pregnancy (see CONTRAINDICATIONS section).

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. If the patient has not had a menstrual period at the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

7. Gallbladder Disease Combination oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Earlier studies have reported an increased relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users is minimal. 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 glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 mcg of ethinyl estradiol or severe glucose intolerance should be discontinued. Some studies indicate that oral contraceptives may cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestogens. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed 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: PRECAUTIONS, 2), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

9. Elevated Blood Pressure An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral-contraceptive users and with continuing use. The physical examination and blood pressure should be monitored periodically. If a significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see CONTRAINDICATIONS section). For most women, elevated blood pressure will return to normal after discontinuation of oral contraceptives. However, there is no difference in the occurrence of hypertension among ever- and never-users.

10. Headache The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe during the use of oral contraceptives and evaluation of the cause. (See WARNINGS, 1c, and CONTRAINDICATIONS.)

11. Bleeding Irregularities Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If bleeding persists or occurs repeatedly, other causes should be considered and diagnosis 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, a change in formulation may be helpful. Women who experience a change in bleeding pattern should be carefully observed. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

12. Ectopic Pregnancy Ectopic as well as intrauterine pregnancy may occur in contraceptive failure. (See WARNINGS, 1c, and CONTRAINDICATIONS.)

PRECAUTIONS 1. General Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

2. Physical Examination and Follow-Up A periodic parous and family medical history and complete physical examination are appropriate for all women, 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 physician. 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 diagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic 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 oral contraceptives. Some progestogens may increase LDL levels and may render the control of hyperlipidemia more difficult. (See WARNINGS, 1a, 1d, and 8.)

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Nonhormonal contraceptive methods should be considered in women with uncontrolled dyslipidemia. Persistent hypertriglyceridemia may occur in a small population of combination oral contraceptive users. Increases of plasma triglycerides may lead to pancreatitis and other complications.

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 Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and with extra care, in patients with conditions which might be aggravated by fluid retention.

6. Emotional Disorders Patients becoming significantly depressed while taking oral contraceptives should stop the medication immediately and seek medical attention. In an attempt to determine whether the symptom is drug related, 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. Gastrointestinal Diarrhea and vomiting may reduce hormone absorption resulting in decreased serum concentrations.

9. Drug Interactions Changes in Contraceptive Effectiveness Associated with Co-administration of Other Products: Contraceptive effectiveness may be reduced when hormonal contraceptives are administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenytoin, phenylethylamine, dexamethasone, carbamazepine, felbamate, fosphenytoin, and zalcitabine, among others. In such cases, a back-up nonhormonal method of birth control should be considered.

Some cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and other penicillins. However, clinical pharmacology studies investigating drug interactions between combined oral contraceptives and these antibiotics have reported inconsistent results. Several of the anti-HIV protease inhibitors have been studied with oral contraceptives. The results of these studies are inconclusive. Increases (and decreases) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral

8. Without spermicides.

9. The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following dosage regimens of oral contraceptives safe and effective for emergency contraception: for tablets containing 50 mcg of ethinyl estradiol and 500 mcg of norgestrel 1 dose is 2 tablets; for tablets containing 20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel 1 dose is 5 tablets; for tablets containing 30 mcg of ethinyl estradiol and 150 mcg of levonorgestrel 1 dose is 4 tablets.

10. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

In a clinical trial with levonorgestrel and ethinyl estradiol tablets, 1,477 subjects had 7,720 cycles of use and a total of 5 pregnancies were reported. This represents an overall pregnancy rate of 0.84 per 100 woman-years. This rate includes patients who did not take the drug correctly. One or more pills were missed during 1,479 (18.8%) of the 7,870 cycles; thus all tablets were taken during 6,391 (81.2%) of the 7,870 cycles. Of the total 7,870 cycles, a total of 150 cycles were excluded from the calculation of the Pearl Index because of the use of backup contraception or missing 3 or more consecutive pills.

CONTRAINDICATIONS Combination oral contraceptives should not be used in women with any of the following conditions: Thrombophlebitis or thromboembolic disorders. A history of deep-vein thrombophlebitis or thromboembolic disorders. Cerebrovascular or coronary artery disease (current or past history). Valvular heart disease with thrombotic complications.

Thrombotic rhythm disorders. Hereditary or acquired angiodysplasia (hemangiomas). Major surgery with prolonged immobilization. Diabetes with vascular involvement. Headaches with focal neurological symptoms. Uncontrolled hypertension. Known or suspected carcinoma of the breast or personal history of breast cancer.

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, or active liver disease. Known or suspected pregnancy. Hypersensitivity to any of the components of Lufeta.

Warnings Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) 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 venous and arterial thrombotic and thromboembolic events (such as thrombophlebitis, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of serious morbidity or mortality increases significantly in the presence of other underlying risk factors such as certain inherited or acquired thrombophilias, hypertension, hyperlipidemia, obesity, diabetes, and surgery or trauma with increased risk of thrombosis (CONTRAINDICATIONS).

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 doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses 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 disease in relation to exposure to a certain factor. Cohort studies provide a measure of the actual incidence of a disease in a population exposed to a certain factor, and 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 a population exposed to a certain factor, and 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 a population exposed to a certain factor, and the difference in the incidence of disease between oral-contraceptive users and nonusers.

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 is about 1.5 for current or former smokers and about 2 to 3 for women who are not smokers. 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 infarction in women in their mid-thirties or older with underlying risk factors. Cohort studies provide a measure of the relative 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 a population exposed to a certain factor, and the difference in the incidence of disease between oral-contraceptive users and nonusers. The reader is referred to a text on epidemiological methods.

2. Venous Thrombosis and Thromboembolism An increased risk of venous thromboembolism has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for venous thromboembolism such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk is about 1.5 for current or former smokers and about 2 to 3 for women who are not smokers. 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 venous thromboembolism in women in their mid-thirties or older with underlying risk factors. Cohort studies provide a measure of the relative 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 a population exposed to a certain factor, and the difference in the incidence of disease between oral-contraceptive users and nonusers. The reader is referred to a text on epidemiological methods.

3. Carcinoma of the Reproductive Organs and Breasts Reproductive and breast cancer are associated with the use of oral contraceptives and the incidence of breast and cervical cancer.

The risk of having breast cancer diagnosed may be slightly increased in current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after combination oral contraceptive discontinuation and by 10 years after cessation the relative risk disappears. However, there continues to be a controversy about the duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have reported a small increase in risk for women who first use combination oral contraceptives at a younger age. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history. However, there continues to be a 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 combination oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. Hepatic Neoplasia Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of these 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. 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) oral-contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision, or other symptoms of retinal vascular disease, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral-Contraceptive Use and Pregnancy Extensive epidemiological studies have revealed no increased risk of birth defects in infants born to women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in relation to cleft lip and palate, when oral-contraceptive use has been discontinued prior to pregnancy. However, there is a small increase in the risk of miscarriage and stillbirth in infants born to women who have used oral contraceptives during pregnancy (see CONTRAINDICATIONS section).

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. If the patient has not had a menstrual period at the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

7. Gallbladder Disease Combination oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Earlier studies have reported an increased relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users is minimal. 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 glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 mcg of ethinyl estradiol or severe glucose intolerance should be discontinued. Some studies indicate that oral contraceptives may cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestogens. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed 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: PRECAUTIONS, 2), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

9. Elevated Blood Pressure An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral-contraceptive users and with continuing use. The physical examination and blood pressure should be monitored periodically. If a significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see CONTRAINDICATIONS section). For most women, elevated blood pressure will return to normal after discontinuation of oral contraceptives. However, there is no difference in the occurrence of hypertension among ever- and never-users.

10. Headache The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe during the use of oral contraceptives and evaluation of the cause. (See WARNINGS, 1c, and CONTRAINDICATIONS.)

11. Bleeding Irregularities Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If bleeding persists or occurs repeatedly, other causes should be considered and diagnosis 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, a change in formulation may be helpful. Women who experience a change in bleeding pattern should be carefully observed. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

12. Ectopic Pregnancy Ectopic as well as intrauterine pregnancy may occur in contraceptive failure. (See WARNINGS, 1c, and CONTRAINDICATIONS.)

PRECAUTIONS 1. General Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

2. Physical Examination and Follow-Up A periodic parous and family medical history and complete physical examination are appropriate for all women, 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 physician. 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 diagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic 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 oral contraceptives. Some progestogens may increase LDL levels and may render the control of hyperlipidemia more difficult. (See WARNINGS, 1a, 1d, and 8.)

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Nonhormonal contraceptive methods should be considered in women with uncontrolled dyslipidemia. Persistent hypertriglyceridemia may occur in a small population of combination oral contraceptive users. Increases of plasma triglycerides may lead to pancreatitis and other complications.

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 Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and with extra care, in patients with conditions which might be aggravated by fluid retention.

6. Emotional Disorders Patients becoming significantly depressed while taking oral contraceptives should stop the medication immediately and seek medical attention. In an attempt to determine whether the symptom is drug related, 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. Gastrointestinal Diarrhea and vomiting may reduce hormone absorption resulting in decreased serum concentrations.

9. Drug Interactions Changes in Contraceptive Effectiveness Associated with Co-administration of Other Products: Contraceptive effectiveness may be reduced when hormonal contraceptives are administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenytoin, phenylethylamine, dexamethasone, carbamazepine, felbamate, fosphenytoin, and zalcitabine, among others. In such cases, a back-up nonhormonal method of birth control should be considered.

Some cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and other penicillins. However, clinical pharmacology studies investigating drug interactions between combined oral contraceptives and these antibiotics have reported inconsistent results. Several of the anti-HIV protease inhibitors have been studied with oral contraceptives. The results of these studies are inconclusive. Increases (and decreases) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral

Special Populations Race Based on the pharmacokinetic study with Lufeta, there are no apparent differences in pharmacokinetic parameters among women of different races.

Hepatic Insufficiency No formal studies have evaluated the effect of hepatic disease on the disposition of Lufeta. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency No formal studies have evaluated the effect of renal disease on the disposition of Lufeta.

Drug-Drug Interactions See PRECAUTIONS section - Drug Interactions

INDICATIONS AND USAGE Lufeta is 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 II 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, the IUD, and Norplant System, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

Table II: Typical Use and Perfect Use of Oral Contraceptives. Columns include Method, Typical Use, and Perfect Use.

Emergency Contraceptive Pills: The FDA has concluded that certain combination oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception. Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.

Use: Trussell, J. Contraceptive Efficacy: In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F. Contraceptive Technology. Seventeenth Revised Edition. New York NY: Irvington Publishers; 1998.

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) 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 8% 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 who rely 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 phase.

7. With spermicidal cream or jelly.

Product Name: Lufeta. Potency: 0.1 mg Levonorgestrel and 0.02 mg Ethinyl Estradiol. Size: 11.1875" x 24. Fold Size: 4.375" x 2.750". Drawing #: Pharm_Fold_20080530.01

Verification: Name/Date Created/Size/Fold size/Mtg. site. Alignment of Tablets & Charts. Superscript & Subscript. Broken Text. Italic Character/Symbols. JDE #, Code 128. Red line if needed. Rev. date. Font: Helvetica Condensed/Condensed Bold. Body Point Size: 6.5 pt. Leading: 6.3 pt. (Charts: 6 pt./6 pt.).

Design by: Date Created: 03/14/12. Proof by: Date: Proof by: Date:

patient is switching from a 28-day regimen of tablets, she should start her first pack of LUTERA on the day after her last tablet. She should not wait any days between packs. On the day you start your first pack of a progestin-only pill and should begin LUTERA the next day. If switching from an implant or injection, the patient should start LUTERA on the day of implant removal or the day of an injection. The day the next injection would be due. In switching from a progestin-only pill, injection, or implant, the patient should be advised to use a nonhormonal back-up method of birth control for the first 7 days of tablet-taking.

If spotting or breakthrough bleeding occurs
If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significant concern. If the bleeding is persistent or prolonged, the patient is advised to consult her physician.
Risk of pregnancy if tablets are missed
While there is little likelihood of ovulation occurring if only one or two white tablets are missed, the possibility of ovulation increases with each successive day that scheduled white tablets are missed. Although the occurrence of pregnancy is unlikely if LUTERA is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.

Use after pregnancy, abortion or miscarriage
LUTERA may be initiated no earlier than day 28 postpartum in the nonlactating mother or after a second trimester abortion due to the increased risk for thromboembolism (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease). The patient should be advised to use a non-hormonal back-up method for the first 7 days of tablet taking.
LUTERA may be initiated immediately after a first trimester abortion or miscarriage, if the patient starts LUTERA immediately, back-up contraception is not needed.

HOW SUPPLIED
LUTERA® tablets (0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol) are available in a 28 Tablet Dispenser, arranged in 3 rows of 7 active tablets and 1 row of inert tablets, as follows:
21 active tablets: white, round tablet debossed with "WATSON" on one side and "949" on the other side.
7 inert tablets: peach, round tablet debossed with "WATSON" on one side and "P1" on the other side.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Brief Summary Patient Package Insert
This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.
Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy, and when taken correctly, have a failure rate of approximately 1.0% per year (1 pregnancy per 100 women per year of use) when used without missing any pills. The average failure rate among numbers of pill users is approximately 5% per year (5 pregnancies per 100 women per year of use) 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 consistently increases the chance 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 life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:
• have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
• have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization.
• have headaches with neurological symptoms.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not 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. 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 not smoking. The following table lists some of the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis) and lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other parts of the body. As with other drugs, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke with oral contraceptives.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
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 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, herbal preparations containing St. John's Wort (Hypericum perforatum), and HIV/AIDS drugs may decrease oral-contraceptive effectiveness.
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.
Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Taking the 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 appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health-care provider.

HOW TO TAKE LUTERA
IMPORTANT POINTS TO REMEMBER
BEFORE YOU START TAKING LUTERA:
1. BE SURE TO READ THESE DIRECTIONS: Before you start taking LUTERA.
And
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. See "WHAT TO DO IF YOU MISS PILLS" below.
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 LUTERA. The problem will usually go away. If it doesn't go away, check with your health-care provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING (within 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA OR IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
Use a back-up nonhormonal method (such as condoms or spermicide) until you check with your health-care provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your health-care provider 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 health-care provider.

BEFORE YOU START TAKING LUTERA
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.
The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 1 week of reminder pack pills (without hormones).
3. FIND:
1. where on the pack to start taking pills, and
2. in what order to take the pills (follow the arrow).

4. BE SURE YOU HAVE READY AT ALL TIMES: ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) to use as a back-up 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. Decide with your health-care provider which is the best day for you. Pick a time of day which will be easy to remember.
DAY 1 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 2 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

2. Take the first "active" white pill of the first pack during the first 24 hours of your period.
3. You will not need to use a back-up nonhormonal method of birth control for the first 7 days, since you are starting the pill at the beginning of your period.
SUNDAY START
1. Take the first "active" white pill of the first pack on the Sunday you start your first pack until the next Sunday (7 days).
2. Use a nonhormonal method of birth control (such as condoms or spermicide) as a backup method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).
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:
Start the next pack on the day after your last "reminder" pill. Do not wait for your period between packs.
IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS
If your previous brand had 21 pills: Wait 7 days to start taking LUTERA. You will probably have your period during that week. Be sure that no more than 7 days pass between the "white" day pack and taking the first white LUTERA pill ("active" with hormone).
If your previous brand had 28 pills: Start taking the first white LUTERA pill ("active" with hormone) on the day after your last reminder pill. Do not wait any days between packs.
WHAT TO DO IF YOU MISS PILLS
LUTERA may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.
If you MISS 1 white "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 COULD BECOME PREGNANT if you have sex in the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.
If you MISS 2 white "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 COULD BECOME PREGNANT if you have sex in the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.
If you MISS 3 OR MORE white "active" pills in a row (during the first 3 weeks):
1. If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
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.
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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.
If you MISS 3 OR MORE white "active" pills in a row (during the first 3 weeks):
1. If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
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.
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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.
If you forget any of the 7 peach "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
If you do not need a back-up nonhormonal birth-control method if you start your next pack on time.
FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED
Use a BACK-UP NONHORMONAL BIRTH-CONTROL METHOD anytime you have sex.

Examples include: smoking, high blood pressure, abnormal lipid levels, certain inherited or acquired clotting disorders, obesity, surgery or injury recent or planned, abortion, prolonged inactivity or bed rest. If possible, combination oral contraceptives should be stopped before surgery and during prolonged inactivity or bedrest.
Cigarette smoking increases the risk of serious cardiovascular events. This risk increases with age and amount of smoking and is quite pronounced in women over 35. Women who use combination oral contraceptives should be strongly advised not to smoke. If you smoke you should talk to your health-care professional before starting combination oral contraceptives.
2. Heart attacks and strokes
Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage 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.
Women with migraine (especially migraine/headache with neurological symptoms) who take oral contraceptives also may be at higher risk of stroke and myocardial infarction (heart attack) (see section WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES).
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. Oral contraceptives may worsen existing gallbladder disease or accelerate the development of gallbladder disease in women previously without symptoms.
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. Although a possible but not definite association has been found with the pill and liver cancers in two studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
5. Cancer of the reproductive organs and breasts
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptives 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 DIFFERENT METHODS OF BIRTH CONTROL, BY AGE, WOMEN, BY FERTILITY-CONTROL METHOD AND 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 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
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 method related
†Deaths are birth related

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.
You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Lipid Metabolism and Triglycerides
There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.
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 serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:
• have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
• have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization.
• have headaches with neurological symptoms.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.
Although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy, nonsmoking women, there are also greater potential health risks associated with pregnancy in older women.
Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not 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. 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 not smoking. The following table lists some of the following medical conditions have been associated with or made worse by the pill:
1. Blood clots in the legs (thrombophlebitis) and lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other parts of the body. As with other drugs, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke with oral contraceptives.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
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 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, herbal preparations containing St. John's Wort (Hypericum perforatum), and HIV/AIDS drugs may decrease oral-contraceptive effectiveness.
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.
Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Taking the 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 appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health-care provider.

HOW TO TAKE LUTERA
IMPORTANT POINTS TO REMEMBER
BEFORE YOU START TAKING LUTERA:
1. BE SURE TO READ THESE DIRECTIONS: Before you start taking LUTERA.
And
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. See "WHAT TO DO IF YOU MISS PILLS" below.
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 LUTERA. The problem will usually go away. If it doesn't go away, check with your health-care provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING (within 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA OR IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
Use a back-up nonhormonal method (such as condoms or spermicide) until you check with your health-care provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your health-care provider 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 health-care provider.

BEFORE YOU START TAKING LUTERA
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.
The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 1 week of reminder pack pills (without hormones).
3. FIND:
1. where on the pack to start taking pills, and
2. in what order to take the pills (follow the arrow).

4. BE SURE YOU HAVE READY AT ALL TIMES: ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) to use as a back-up 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. Decide with your health-care provider which is the best day for you. Pick a time of day which will be easy to remember.
DAY 1 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 2 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 3 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 4 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 5 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 6 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 7 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 8 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

DAY 9 START
1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip step #1.

Examples include: smoking, high blood pressure, abnormal lipid levels, certain inherited or acquired clotting disorders, obesity, surgery or injury recent or planned, abortion, prolonged inactivity or bed rest. If possible, combination oral contraceptives should be stopped before surgery and during prolonged inactivity or bedrest.
Cigarette smoking increases the risk of serious cardiovascular events. This risk increases with age and amount of smoking and is quite pronounced in women over 35. Women who use combination oral contraceptives should be strongly advised not to smoke. If you smoke you should talk to your health-care professional before starting combination oral contraceptives.
2. Heart attacks and strokes
Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage 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.
Women with migraine (especially migraine/headache with neurological symptoms) who take oral contraceptives also may be at higher risk of stroke and myocardial infarction (heart attack) (see section WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES).
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. Oral contraceptives may worsen existing gallbladder disease or accelerate the development of gallbladder disease in women previously without symptoms.
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. Although a possible but not definite association has been found with the pill and liver cancers in two studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
5. Cancer of the reproductive organs and breasts
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptives 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 DIFFERENT METHODS OF BIRTH CONTROL, BY AGE, WOMEN, BY FERTILITY-CONTROL METHOD AND 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 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
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 method related
†Deaths are birth related

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.
You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Lipid Metabolism and Triglycerides
There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.
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 serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:
• have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
• have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization.
• have headaches with neurological symptoms.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.
Although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy, nonsmoking women, there are also greater potential health risks associated with pregnancy in older women.
Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not 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. 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 not smoking. The following table lists some of the following medical conditions have been associated with or made worse by the pill:
1. Blood clots in the legs (thrombophlebitis) and lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other parts of the body. As with other drugs, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke with oral contraceptives.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
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 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, herbal preparations containing St. John's Wort (Hypericum perforatum), and HIV/AIDS drugs may decrease oral-contraceptive effectiveness.
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.
Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Lipid Metabolism and Triglycerides
There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.
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 serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:
• have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
• have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization.
• have headaches with neurological symptoms.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.
Although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy, nonsmoking women, there are also greater potential health risks associated with pregnancy in older women.
Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not 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. 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 not smoking. The following table lists some of the following medical conditions have been associated with or made worse by the pill:
1. Blood clots in the legs (thrombophlebitis) and lungs (pulmonary embolism), blockage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other parts of the body. As with other drugs, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke with oral contraceptives.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
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 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, herbal preparations containing St. John's Wort (Hypericum perforatum), and HIV/AIDS drugs may decrease oral-contraceptive effectiveness.
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.
Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.
After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill or by the fact that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.
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.
Taking the 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 appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health-care provider.

HOW TO TAKE LUTERA
IMPORTANT POINTS TO REMEMBER
BEFORE YOU START TAKING LUTERA:
1. BE SURE TO READ THESE DIRECTIONS: Before you start taking LUTERA.
And
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. See "WHAT TO DO IF YOU MISS PILLS" below.
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 LUTERA. The problem will usually go away. If it doesn't go away, check with your health-care provider.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up for missed pills, you could



BRIEF SUMMARY
PATIENT PACKAGE INSERT
 This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING
Lutera®
 (Levonorgestrel and Ethinyl Estradiol Tablets USP)
 Rx only

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 leaflet 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 leaflet is not a replacement for a careful discussion between you and your health-care provider. You should discuss the information provided in this leaflet 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
 Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than most other nonsurgical methods of birth control. When they are taken correctly, without missing any pills, the chance of becoming pregnant is approximately 1% per year (1 pregnancy per 100 women per year of use). Typical failure rates are approximately 5% per year (5 pregnancies per 100 women per year of use) when women who miss pills are included. The chance of becoming pregnant increases with each missed pill during each 28-day cycle of use. In comparison, average failure rates for other methods of birth control during the first year of use are as follows:

IUD: 0.1-2%	Female condom alone: 21%
Depo-Provera® (injectable progestogen): 0.3%	Cervical cap
Norplant® System (levonorgestrel implants): 0.05%	Never given birth: 20%
Diaphragm with spermicides: 20%	Given birth: 40%
Spermicides alone: 26%	Periodic abstinence: 25%
Male condom alone: 14%	No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES
 Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Some women should not use the pill. For example, you should not take the pill if you have any of the following conditions:

- 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, or certain hormonally-sensitive cancers.
- Unexplained vaginal bleeding (until a diagnosis is reached by your health-care provider).
- Liver tumor (benign or cancerous) or active liver disease.
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill.
- Known or suspected pregnancy.
- A need for surgery with prolonged bedrest.
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots.
- Diabetes affecting your circulation.
- Headaches with neurological symptoms.
- Uncontrolled high blood pressure.
- Allergy or hypersensitivity to any of the components of LUTERA (levonorgestrel and ethinyl estradiol tablets).

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES
 Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram.
- Diabetes.
- Elevated cholesterol or triglycerides.
- High blood pressure.
- A tendency to form blood clots.
- Migraine or other headaches or epilepsies.
- Depression.
- Gallbladder, liver, 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 health-care provider if you smoke or are on any medications.

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

RISKS OF TAKING ORAL CONTRACEPTIVES
 1. *Risks of developing blood clots*
 Blood clots and blockage of blood vessels are 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.

Users of combination oral contraceptives have a higher risk of developing blood clots compared to non-users. This risk is highest during the first year of combination oral-contraceptive use.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or injury, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your health-care provider about stopping oral contraceptives three to 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 or after a trimester pregnancy termination. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section *While breast-feeding in GENERAL PRECAUTIONS.*)

The risk of blood clots is greater in users of combination oral contraceptives compared to nonusers. This risk may be higher in users of high-dose pills (those containing 50 mcg or more of estrogen) and may also be greater with longer use. In addition, some of these increased risks may continue for a number of years after stopping combination oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of combination oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages.

The excess risk of blood clots is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is lower than blood clots associated with pregnancy. The use of combination oral contraceptives also increases the risk of other clotting disorders, including heart attack and stroke. Blood clots in veins cause death in 1% to 2% of cases. The risk of clotting is further increased in women with other conditions. Examples include: smoking, high blood pressure, abnormal lipid levels, certain inherited or acquired clotting disorders, obesity, surgery or injury, recent delivery or second trimester abortion, prolonged inactivity or bed rest. If possible, combination oral contraceptives should be stopped before surgery and during prolonged inactivity or bedrest.

Cigarette smoking increases the risk of serious cardiovascular events. This risk increases with age and amount of smoking and is quite pronounced in women over 35. Women who use combination oral contraceptives should be strongly advised not to smoke. If you smoke you should talk to your health care professional before taking combination oral contraceptives.

2. *Heart attacks and strokes*
 Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage 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.

Women with migraine (especially migraine/headache with neurological symptoms) who take oral contraceptives also may be at higher risk of stroke and must not use combination oral contraceptives (see section **WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES**).

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. Oral contraceptives may worsen existing gallbladder disease or accelerate the development of gallbladder disease in women previously without symptoms.

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, a possible but not definite association has been found with the pill and liver cancers in two studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. *Cancer of the reproductive organs and breasts*
 Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.

After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.

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.

6. *Lipid Metabolism and Pancreatitis*
 There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.

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 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD AND 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 nonsmoker**	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

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 to 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, except for those women over the age of 40, when 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 high-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral-contraceptive use by healthy, nonsmoking women over 40 years of age may outweigh the possible risks. 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 the individual patient needs.

WARNING SIGNALS
 If any of these adverse effects occur while you are taking oral contraceptives, call your health-care provider 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 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. *Unscheduled or breakthrough vaginal bleeding or spotting*
 Unscheduled vaginal bleeding or spotting may occur while you are taking the pills. Unscheduled bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unscheduled 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 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 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 health-care provider.

4. *Melasma*
 A spotty darkening of the skin is possible, particularly of the face.

5. *Other side effects*
 Other side effects may include nausea, breast tenderness, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, inflammation of the pancreas, and allergic reactions.

If any of these side effects bother you, call your 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

Product Name **Lutera** Potency _____ Size: **21.75" x 10"** Fold Size: **1.75" x 3.125"**

PATIENT INSERT MED GUIDE PHYSICIAN INSERT

Verification of Insert/Med Guide

Heading: Name/Date Created/ Size/Fold size/Mfg. site Alignment of Tablets & Charts Superscript & Subscript Broken Text

Italic Character/Symbols JDE #, Code 128 Red line if needed Rev. date

Font **Helvetica Condensed/Condensed Bold** Body Point Size: **8.5 pt.** Leading: **8.5 pt.**

Design by _____ Date Created: **03/14/2012** Proof by: _____ Date: _____ Proof by: _____ Date: _____

