Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg

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, light yellow tablet (21) contains 0.1 mg of levonorgestrel, d(-)-13β-ethyl-17-ethyl-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, ferric oxide of iron (yellow), ferric oxide of iron (red), lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K-25, and sodium lauryl sulfate.

Each inactive, brown tablet (7) contains the following inactive ingredients: croscarmellose sodium, ferric oxide of iron (brown), lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone K-25.

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 reduce the likelihood of implantation).

Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel and ethinyl estradiol tablets in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed following oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract 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 levonorgestrel and ethinyl estradiol tablets 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, attained from 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, attained from at least day 6 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 (SE) levonorgestrel and ethinyl estradiol serum concentrations in 22 subjects receiving levonorgestrel and ethinyl estradiol tablets (100 µg levonorgestrel and 20 µg ethinyl estradiol)

Table I provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

| TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF LEVONORGESTREL AND ETHINYL ESTRADIOL TABLETS OVER A 21-DAY DOSING PERIOD |
| Day | Cmax ng/mL | Tmax h | AUC(0-∞) ng*h/mL | CL/F ml/min | Vb/f L/kg | SHBG nmol/L |
| 1 | 2.75 (0.88) | 1.6 (0.9) | 38.2 (12.8) | 53.2 (20.8) | 2.96 (1.09) | 57 (19) |
| 6 | 4.52 (1.79) | 1.5 (0.7) | 40.6 (18.6) | 40.8 (15.8) | 2.00 (0.96) | 81 (26) |
| 21 | 6.00 (2.66) | 1.5 (0.5) | 68.3 (32.5) | 68.4 (13.3) | 1.43 (0.62) | 93 (40) |

Distribution

Ethinyl estradiol is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.
Emergency Contraceptive Pills: The FDA has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestimate 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%.


1. Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who use it correctly for an entire menstrual cycle (5 to 7 days if they do not stop use for any other reason.
2. Among couples who initiated use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

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

4. The percent 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, 85% become pregnant within one year. This estimate was slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

5. Foams, creams, gels, vaginal suppositories, and vaginal rings were not used in this study.

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

7. With spermicidal cream or jelly.

8. Without spermicides.

9. Not available in all countries.

10. To maintain effective protection against pregnancy, another method of contraception must be used as well as non-contraception.

CONTRAINDICATIONS

Combination oral contraceptives should not be used in women with any of the following conditions:

- Thromboembolic disorders or thrombotic disorders
- A history of deep-vein thrombophlebitis, or thromboembolic disorders as determined in the medical evaluation.
- Cerebrovascular or coronary artery disease (current or past history).
- Valvular heart disease with thrombogenic complications
- Thrombogenic manifestations during pregnancy
- Hereditary or acquired thrombophilia
- 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 in a patient with prior pill use
- Hepatic adenomas or carcinomas, or active liver disease
- Known or suspected pregnancy
- Hypersensitivity to any of the components of levonorgestrel and ethinyl estradiol tablets

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk is highest in women with an extensive smoking history (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 thromboembolic events (such as myocardial infarction, 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 morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited or acquired thrombophilia, hypertension, hyperlipidemias, obesity, diabetes, and surgery or trauma with increased risk of thrombosis (see CONTRAINDICATIONS).

Pretreatment 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, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. This is very low under the age of 50. 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 smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (FIGURE II) among women who use oral contraceptives.

CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS

<table>
<thead>
<tr>
<th>AGE</th>
<th>EVER-USERS (NONSMOKERS)</th>
<th>EVER-USERS (SMOKERS)</th>
<th>CONTROLS (NONSMOKERS)</th>
<th>CONTROLS (SMOKERS)</th>
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<td>15-24</td>
<td>200</td>
<td>200</td>
<td>40</td>
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<tr>
<td>25-34</td>
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<td>20</td>
</tr>
<tr>
<td>45-65</td>
<td>50</td>
<td>50</td>
<td>10</td>
<td>10</td>
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</tbody>
</table>

FIGURE II: (Adapted from P.M. Layde and V. Beral, Lancet, 1:541-546, 1981.)

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

b. Venous thrombosis and thromboembolism

An increased risk of venous thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low (≤50 mcg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5 to 10,000 woman-years for non-users. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. Venous thromboembolism may be fatal. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and gradually disappears after pill use is stopped.

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

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonusers who used oral contraceptives, 2.5 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for nonnormotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilia. Women with migraine (particularly migraine/headaches with focal neurological symptoms, see CONTRAINDICATIONS) who take combination oral contraceptives may be at an increased risk of stroke.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of oral contraceptives depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Exposing minimum to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

e. Persistence of risk of vascular disease

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

2. Estimates of Mortality from Contraceptive Use
One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 and with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

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Therefore, the Committee recommended that the benefits of oral-contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

### TABLE III: 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

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>No fertility - control method*</td>
<td>7.0</td>
<td>7.4</td>
<td>9.1</td>
<td>14.8</td>
<td>25.7</td>
<td>28.2</td>
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<tr>
<td>Oral contraceptives</td>
<td></td>
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<tr>
<td>nonsmoker**</td>
<td>0.3</td>
<td>0.5</td>
<td>0.9</td>
<td>1.9</td>
<td>13.8</td>
<td>31.6</td>
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<tr>
<td>Oral contraceptives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoker**</td>
<td>2.2</td>
<td>3.4</td>
<td>6.6</td>
<td>13.5</td>
<td>31.1</td>
<td>117.2</td>
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<tr>
<td>IUD*</td>
<td>0.8</td>
<td>0.8</td>
<td>1.0</td>
<td>1.0</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Condom*</td>
<td>1.1</td>
<td>1.6</td>
<td>0.7</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Diaphragm/spерmacide*</td>
<td>1.9</td>
<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Periodic abstinence*</td>
<td>2.5</td>
<td>1.6</td>
<td>1.6</td>
<td>1.7</td>
<td>2.9</td>
<td>3.6</td>
</tr>
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</table>

* Deaths are birth related
** Deaths are method related
Adapted from H.W. Ory, Family Planning Perspectives, 15: 57-63, 1983.

3. Carcinoma of the Reproductive Organs and Breasts
Numerous epidemiological studies have examined the association between the use of oral contraceptives and the incidence of breast and cervical cancer.

The risk of having breast cancer diagnosed may be slightly increased among 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 increased risk disappears. Some studies report an increased risk with 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 or her family breast cancer history.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers. Women with known or suspected carcinoma of the breast or personal history of breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between 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 can result in fatal 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.

5. Ocular Lesions
There have been a few case reports of retinal thrombosis associated with the use of oral contraceptives

6. Oral-Contraceptive Use Before or During Early Pregnancy
Periodic abstinence* and contraceptive failures. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

7. Gallbladder Disease
Combination oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previous asymptomatic women. Earlier studies have reported an increased lifetime 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 may be minimal. The reported 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 estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resis-
Libido, change in
Lactation, diminution in, when given immediately postpartum
Infertility after discontinuation of treatment, temporary
Hirsutism
Erythema multiforme
Edema/fluid retention
Dizziness
Corneal curvature (steepening), change in
Contact lenses, intolerance to
Colitis
Cholestatic jaundice
and circulatory symptoms
Amenorrhea
to be drug related (alphabetically listed):
The following adverse reactions have been reported in patients receiving oral contraceptives and are believed
retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and
breasts, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including
Thromboembolic and thrombotic disorders and other vascular problems (including thrombophlebitis and
mation) has been associated with the use of oral contraceptives:
An increased risk of the following serious adverse reactions (see
sections.
16. Information for the Patient
See Patient Labeling Printed Below.
ADVERSE REACTIONS
An increased risk of the following serious adverse reactions (see WARNINGS section for additional infor-
mation) has been associated with the use of oral contraceptives:
Thromboembolic and thrombotic disorders and other vascular problems (including thrombophlebitis and
venous thrombosis with or without pulmonary embolism, mesenteric thrombosis, arterial thromboembolism,
myocardial infarction, cerebral hemorrhage, cerebral thrombosis), carcinoma of the reproductive organs and
breasts, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including
retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and
headache including migraine.
The following adverse reactions have been reported in patients receiving oral contraceptives and are believed
to be drug related (alphabetically listed):
Acne
Amenorrhea
Anaphylactic/anaphylactoid reactions, including urticaria, angioedema and severe reactions with respiratory
and circulatory symptoms
Breast changes: tenderness, pain, enlargement, secretion
Budd-Chiari syndrome
Cervical erosion and secretion, change in
Cholestatic jaundice
Chorea, exacerbation of
Colitis
Contact lenses, intolerance to
Corneal curvature (steepening), change in
Dizziness
Edema/fluid retention
Ethythma multiforme
Erythema nodosum
Gastrointestinal symptoms (such as abdominal pain, cramps, and bloating)
Hinutism
Infertility after discontinuation of treatment, temporary
Lactation, diminution in, when given immediately postpartum
Libido, change in
Melaena/chloasma which may persist
Menstrual flow, change in
Mood changes, including depression
Nausea
Nervousness
Pancreatitis
Porphyria, exacerbation of
Rash (allergic)
Scalp hair, loss of
Serum folate levels, decrease in
Spotting
Systemic lupus erythematosus, exacerbation of
Unscheduled bleeding
Vaginitis, including candidiasis
Varicose veins, aggravation of
Vomiting
Weight or appetite (increase or decrease), change in
The following adverse reactions have been reported in patients of oral contraceptives:
Cataracts
Cystitis-like syndrome
Dysmenorrhea
Hemolytic uremic syndrome
Hemorrhagic eruption
Optic neuritis, which may lead to partial or complete loss of vision
Premenstrual syndrome
Renal function, impaired
OVERDOSAGE
Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, and drowni-
ness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of
overdose, if necessary, is directed to the symptoms.
NONPREVENTIVE HEALTH BENEFITS
The following noncontraceptive health benefits related to the use of oral contraceptives are supported by
epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding
0.035 mg of ethinyl estradiol or 0.05 mg of mestranol. Effects on menses:
Increased menstrual cycle regularity
Decreased blood loss and decreased incidence of iron-deficiency anemia
Decreased incidence of dysmenorrhea
Effects related to inhibition of ovulation:
Decreased incidence of functional ovarian cysts
Decreased incidence of ectopic pregnancies
Effects from long-term use:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast
Decreased incidence of acute pelvic inflammatory disease
Decreased incidence of endometrial cancer
Decreased incidence of ovarian cancer
DOSEAGE AND ADMINISTRATION
To achieve maximum contraceptive effectiveness, Aubra (levonorgestrel and ethinyl estradiol tablets) must be
taken exactly as directed and at intervals not exceeding 24 hours. The dosage of Aubra is one light yellow
tablet daily for 21 consecutive days, followed by one brown inert tablet daily for 7 consecutive days, accord-
ing to the prescribed schedule. It is recommended that Aubra tablets be taken at the same time each day.
During The First Cycle Of Use
The possibility of ovulation and conception prior to initiation of medication should be considered. The patient
should be instructed to begin taking Aubra on either the first Sunday after the onset of menstruation (Sunday Start)
or on Day 1 of menstruation (Day 1 Start).
Sunday start
The patient is instructed to begin taking Aubra on the first Sunday after the onset of menstruation. If men-
struation begins on a Sunday, the first tablet (light yellow) is taken that day. One light yellow tablet should be
taken daily for 21 consecutive days, followed by one brown inert tablet daily for 7 consecutive days.
Withdrawal bleeding should usually occur within 3 days following discontinuation of light yellow tablets and
may not have finished before the next pack is started. During the first cycle, contraceptive reliance should not be
placed on Aubra until a light yellow tablet has been taken daily for 7 consecutive days, and a nonhormonal back-up
method of birth control should be used during those 7 days.
Day 1 start
During the first cycle of medication, the patient is instructed to begin taking Aubra during the first 24 hours of
her period (day one of her menstrual cycle). One light yellow tablet should be taken daily for 21 consecutive
days, followed by one brown inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually
occur within 3 days following discontinuation of light yellow tablets and may not have finished before the next
pack is started. If medication is begun on day one of the menstrual cycle, no back-up contraception is
necessary. If Aubra tablets are started later than day one of the first menstrual cycle or postpartum, contracep-
tive reliance should not be placed on Aubra tablets until after the first 7 consecutive days of administration,
and a nonhormonal back-up method of birth control should be used during those 7 days.
After the first cycle of use
The patient begins her next and all subsequent courses of tablets on the day after taking her last brown tablet.
She should follow the same dosing schedule: 21 days on light yellow tablets followed by 7 days on brown
Tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against
pregnancy by using a nonhormonal back-up method of birth control until she has taken a light yellow tablet
daily for 7 consecutive days.
Switching from another hormonal method of contraception
When the patient is switching from a 21-day regimen of tablets, she should wait 7 days after her last tablet
before she starts Aubra. She will probably experience withdrawal bleeding during that week. She should be
sure that she does not miss any tablets. If she misses a tablet, she should take it as soon as she remembers it
and continue with the regular dose schedule. If she misses 2 or more tablets, she should start a new cycle on
the 5th day after missing the last tablet she took, and she should take 7 tablets daily for 7 consecutive days.
If there is any delay in restarting Aubra tablets, it is recommended that she use back-up contraception (e.g.,
barrier method) for the first 7 days of Aubra tablets-taking.

4
If spotting or breakthrough bleeding occurs
If spotting or breakthrough bleeding occur, the patient is instructed to continue on the same regimen. This type of bleeding usually occurs without significant consequences; however, 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 light yellow tablets are missed, the possibility of ovulation increases with each successive day that scheduled light yellow tablets are missed. Although the occurrence of pregnancy is unlikely if AUBRA 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 regimen and misses two consecutive periods, pregnancy should be ruled out.

The risk of pregnancy increases with each active (light yellow) tablet missed. For additional patient instructions regarding missed tablets, see the WHAT TO DO IF YOU MISS PILLS section in the DETAIL PATIENT LABELING below.

Use after pregnancy, abortion or miscarriage
Aubra 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 backup method for the first 7 days of tablet taking. Aubra may be initiated immediately after a first trimester abortion or miscarriage. If the patient starts Aubra immediately, back-up contraception is not needed.

HOW SUPPLIED
Aubra tablets (0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol) are available in a 28 Tablet Blister, arranged in 4 rows of 7 active tablets and 1 row of inert tablets, as follows:
21 active tablets: light yellow colored, uncoated, round, unscored, flat tablets debossed with 201 on one side and blank on the other side.
7 inert tablets: brown colored, uncoated, un-scored flat tablets debossed with 271 on one side and blank on the other side.
Aubra tablets are available as follows:
Monocarton NDC 50102-120-01
Clinical Pack NDC 50102-120-48 (48 Monocartons)
Shipper/Case NDC 50102-120-90 (3 Clinical Packs/144 Monocartons)
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 correctly used, 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 of large 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 women using oral contraceptives as are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy. For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:
- smoke
- have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
- have or have had clots or embolism, 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 an 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. These side effects, especially nausea and vomiting, may subside within the first three months of use.
The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill.
1. Blood clots in the legs (thrombophlebitis) 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 organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraines also may be at increased risk of stroke with pill use.
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 label given to you with your supply of Aubra. 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.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if 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 nodules or other abnormalities diagnosed. If you currently have or have had breast cancer, you 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 AUBRA

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING AUBRA

1. BE SURE TO READ THESE DIRECTIONS: Before you start taking AUBRA,
   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 the AUBRA. 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 these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING (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 AUBRA

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” light yellow pills (with hormones) to take for 3 weeks, followed by 1 week of reminder brown 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 arrows).

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 blister.
2. Decide with your health-care provider which is the best day for you. Pick a time of day which will be easy for you.
3. 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 blister.
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.

You must start taking the pill at least 24 hours after you start your first pack until the next Sunday (7 days).

AUBRA (levonorgestrel and ethinyl estradiol tablets) 0.1 mg/0.02 mg (201 tablets in 28 blister packs, b and s pharmaceuticals)
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 any days between packs.
IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS
If your previous brand had 21 pills, you will start taking AUBRA 7 days after finishing the last light yellow AUBRA pill (“active” with hormone). In comparison, average failure rates for other methods of birth control during the first year of use are as follows:

- Male condom alone: 14%
- Female condom alone: 21%
- Diaphragm with spermicides: 20%
- Norplant® System (levonorgestrel implant): 0.05%
- Depo-Provera® (injectable progestogen): 0.3%
- Cervical cap
- Never given birth: 20%
- Spermicides alone: 26%
- Given birth: 40%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES
Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with 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.

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.
- Yeasting 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 AUBRA (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 epilepsy.
- 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 use 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 soon after delivery of a baby or after a midtrimester 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 bed rest. If you are taking combination oral contraceptives, you should be advised not to smoke.

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.
Deaths are birth related

• 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 eyelids, 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
Sudden vaginal bleeding or spotting may occur while you are taking the pill. 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 it may also occur later if 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 and ankles and may raise your blood pressure. If you experience fluid retention, contact your health-care provider.

4. Melisma
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, diziness, loss of scalp hair, rash, vaginal infections, inflammation of the pancreas and allergic reaction. 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 a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health-care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health-care provider immediately to determine whether you are pregnant. Stop taking oral contraceptives if you are pregnant.

There is no conclusive evidence that oral-contraceptive use is associated with an increase in birth defects, when taking contraceptives concurrently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives should not be used during pregnancy. You should check with your health-care provider about risks to your unborn child of any medication taken during pregnancy.

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

You should consider starting oral contraceptives only after you have weaned your child completely.

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

4. Drug interactions
Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital and phenytoin sodium) and the anti-HIV drug (Protease inhibitor) (one brand of this drug), prindolone (Mysoline®), toipiramate (Topamax®), carbamazepine (Tegretol®) and possibly certain antibiotics (such as amoxicillin and other penicillins, and tetracyclines), and herbal products containing St. John’s Wort (Hypericum perforatum). You may also need to use a nonoral method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

You may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.

You should inform your health-care provider about all medicines you are taking, including nonprescription products.

5. Sexually transmitted diseases
This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE AUBRA

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING AUBRA:

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

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME. If you miss your 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 start taking AUBRA. 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 these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING (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, contact your health-care provider.

BEFORE YOU START TAKING AUBRA

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” light yellow pills (with hormones) to take for 3 weeks, followed by 1 week of reminder brown 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 arrows).

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 blister. Note: if the first day of your period is a Sunday, you can skip step #1.

2. Take the first “active” light yellow 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, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first “active” light yellow pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

2. Use a nonhormonal method of birth control (such as condoms or spermicide) as a backup method if you have sex anytime after 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).

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

3. When you finish a pack:
   1. Start the next pack on the day after your last “reminder” pill. Do not wait any days between packs.

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS

If your previous brand had 21 pills: Wait 7 days to start taking AUBRA. You will probably have your period during that week. Be sure that no more than 7 days pass between the 21-day pack and taking the first light yellow AUBRA pill (“active” with hormone).

If your previous brand had 28 pills: Start taking the first light yellow AUBRA 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

AUBRA may not be as effective if you miss light yellow “active” pills, and particularly if you miss the first few or the last few light yellow “active” pills in a pack.

If you MISS 1 light yellow “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 light yellow “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 2 light yellow “active” pills in a row in THE 3RD WEEK:

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

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

   If you are a Day 1 Starter:
   1. If you are a Day 1 Starter:
   2. Take the pill pack to your health-care provider.

   If you are a Sunday Starter:
   1. 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 light yellow “active” pills in a row (during the first 3 weeks):

   1. If you are a Day 1 Starter:
   2. If you are a Day 1 Starter:

   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 brown “reminder” pills in Week 4:

   1. You do not need a back-up nonhormonal birth-control method if you start your next pack on time.

   FINALY, 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. KEEP TAKING ONE PILL EACH DAY until you can reach your health-care provider.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately 1 per year (1 pregnancy per 100 women per year of use) if taken every day as directed, but the more typical failure rate is approximately 5% per year (5 pregnancies per 100 women per year of use) including women who do not always take the pill exactly as directed without missing any pills. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your health-care provider.

PREGNANCY AFTER STOPPING THE PILL

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

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

BIRTH CONTROL AFTER STOPPING THE PILL

If you do not wish to become pregnant after stopping the pill, you should use another method of birth control immediately after stopping AUBRA. Speak to your health-care provider about another method of birth control.

OVERDOSAGE

Overdose may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain and fatigue/drowsiness. Withdrawal bleeding may occur in females. In case of overdose, contact your health-care provider or pharmacist.

OTHER INFORMATION

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

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

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ecstopy (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your health-care provider or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

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