CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75256_S3

DRAFT FINAL PRINTED LABELING
DESCRIPTION

Apr 28 and 21 Day Regimen bilayer tablets for desogestrel and ethinyl estradiol tablets provide an oral contraceptive regimen of 21 days of active tablets followed by 7 days of inactive tablets. The active ingredient in each tablet is desogestrel and ethinyl estradiol. The inactive ingredients include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, talc, and black ink. Each tablet contains 0.15 mg desogestrel (9-ethyl-17α-ethylnormestrone-18,19-dione-17β-piperazine-4-ene-20α-methyl-17β-oxy) and 0.03 mg ethinyl estradiol (19-nor-17α-ethynylestrone-3,17-diol). The inactive ingredients include colloidal silicon dioxide, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, talc, and black ink.

CLINICAL PHARMACOLOGY

Pharmacokinetics

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 changes in the endometrium which reduce the likelihood of implantation.

Receptor binding studies, as well as studies in animals and humans, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progesterational activity with minimal androgynic and oestrogenic activity (61,52). Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone (56-69).

Pharmacotherapeutics

Desogestrel is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, a biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of 3-keto-desogestrel, is approximately 64%.

In the third cycle of use after a single desogestrel and ethinyl estradiol tablet, maximum concentrations of 3-keto-desogestrel of 2.380 ± 1.302 ng/mL (mean ± SD) are reached at 1.4 ± 0.6 hours. The area under the curve (AUC0-∞) in 3.356 ± 1.145 ng·h/mL at a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of 3-keto-desogestrel of 2.496 ± 0.267 ng/mL, are reached at 1.4 ± 0.6 hours. The minimum plasma levels of 3-keto-desogestrel at steady state are 1.400 ± 0.569 ng/mL. The AUC0-∞ at steady state is 3.209 ± 0.175 ng·h/mL. The mean AUC0-∞ for 3-keto-desogestrel at single dose is significantly lower than the mean AUC0-∞ at steady state. This indicates that the kinetics of 3-keto-desogestrel are non-linear due to an increase in binding to sex hormone-binding globulin levels which are induced by the daily administration of ethinyl estradiol. Sex hormone-binding globulin levels increased significantly in the third treatment cycle from day 1 (104±48 ng/mL) to day 21 (230±69 nmol/L).

The elimination half-life for 3-keto-desogestrel is approximately 36±20 hours at steady state. In addition to 3-keto-desogestrel, other phase I metabolites are 3-OH-desogestrel, 36-OH-desogestrel, and 3-OH-36-OH-desogestrel. These other metabolites are not known to have any pharmacological effects, and are further converted in our by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides.

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single desogestrel and ethinyl estradiol tablet, the relative bioavailability is approximately 65%.

In the third cycle of use after a single desogestrel and ethinyl estradiol tablet, maximum concentrations of ethinyl estradiol of 95±34 ng/mL, are reached at 1.5 ± 0.8 hours. The AUC0-∞ in 1.471 ± 0.658 ng·h/mL at a single dose. At steady state, attained from at least day 19 onwards, maximum cerebral estradiol concentrations of 114±14 ng/mL, are reached at 1.4 ± 0.7 hours. The minimum plasma levels of ethinyl estradiol at steady state are 74.8±5.2 ng/mL. The AUC0-∞ at steady state is 1.117 ± 0.205 ng·h/mL.

The mean AUC0-∞ for ethinyl estradiol following a single dose during treatment cycle 3 does not significandy differ from the mean AUC0-∞ at steady state. This indicates linear kinetics for ethinyl estradiol.

The elimination half-life is 35±8 hours at steady state. Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase I metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes phase II metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

INDICATIONS AND USAGE
April (desogestrel and ethinyl estradiol) Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Oral contraceptives are highly effective. Table 1 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

<table>
<thead>
<tr>
<th>Method</th>
<th>Lowest</th>
<th>Typical††</th>
</tr>
</thead>
<tbody>
<tr>
<td>(No Contraceptives)</td>
<td>(85)</td>
<td>(85)</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>combined</td>
<td>0.1</td>
<td>N/A††</td>
</tr>
<tr>
<td>progestin-only</td>
<td>0.5</td>
<td>N/A††</td>
</tr>
<tr>
<td>Diaphragm with spermicidal</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>cream or jelly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spermicides alone (Foams,</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>creams, gels, jelly vaginal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>suspensions, and vaginal films)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Sponge</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>nuptora</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>norplant</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>implant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>injection depot</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>medroxyprogesterone acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>progestrone</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>copper T 380A</td>
<td>0.6</td>
<td>0.8</td>
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<td>Condom without spermicides</td>
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<td></td>
</tr>
<tr>
<td>female</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>male</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Cervical Cap with spermicidal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cream or jelly</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>nuptora</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>periocid elastrene (all methods)</td>
<td>1-9</td>
<td></td>
</tr>
<tr>
<td>Female sterilization</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Male sterilization</td>
<td>0.10</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Adapted from RA Hatcher et al., Table 5-2, (1994) ref. #1.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.

†† This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

† N/A — Data not available.

In a clinical trial with desogestrel and ethinyl estradiol tablets, 1,195 subjects completed 11,656 cycles and a total of 10 pregnancies were reported. This represents an overall user-effectiveness (typical user-effectiveness) pregnancy rate of 1.12 per 100 woman-years. This rate includes patients who did not take the drug correctly.

CONTRAINDICATIONS

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

- Thromboembolism or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Central vascular or coronary artery disease
- Known or suspected cancers at the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasms
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior oil use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

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

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

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is primarily based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogen and progesterone than those in common use today. The effect of long term use of the oral contraceptives with formulations of lower doses of both estrogens and progesterone remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonsmokers. 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 nonsmokers. The attributable risk does provide information about the actual occurrence of a disease in the population. (Adapted from
1. MYOCARDIAL INFARCTION

A decreased 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, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (4:10). The risk is very low in women under the age of 30.

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

**Table II.** Cardiovascular disease mortality rates per 100,000 women-years by age, smoking status and oral contraceptive use.

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-Smokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>25-34</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>35-44</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>45-54</td>
<td>125</td>
<td>250</td>
</tr>
</tbody>
</table>

(Adapted from P.M. Layde and V. Beran, ref. #13.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemia, and obesity (13). In particular, some progestins are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may increase the risk of myocardial infarction (14-19). 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.

Contraceptives have minimal androgenic activity (See CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater (10). (b)

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Data from case-control and cohort studies report that oral contraceptives containing desogestrel (Apro-Des (desogestrel and ethinyl estradiol) tablets contain desogestrel) are associated with a two-fold increase in the risk of venous thromboembolic disease as compared to other low-dose (containing less than 50 mg of estrogen) pills containing other progestins. According to these studies, this two-fold risk increases the yearly occurrence of venous thromboembolic disease by about 10-15 cases per 100,000 women.

Earlier case control studies on older formulations 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 (2,3,19-24). Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization (25). The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped (2).

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives (5). The relative risk of venous thromboembolism in women who have predisposing conditions is twice that of women without such medical conditions (25), if feasible, oral contraceptives should be discontinued at least four weeks prior to and for
two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed.

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

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension (30). The relative risk of hemorrhagic stroke is reported to be 1.3 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.8 for smokers who used oral contraceptives, 1.8 for non-motivational users and 25.7 for users with severe hypertension (30). The attributable risk is also greater in older women (3).

d. Dose-related risk of vascular disease from oral contraceptives
A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease (31-33). A decline in serum high density lipoprotein (HDL) has been reported with many progestational agents (14-16). A decline in serum high density lipoprotein has been associated with an increased incidence of atherothrombotic disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

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

e. Persistence of risk of vascular disease
There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives, in a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years old who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in either age groups (33). In another study in Great Britain, the risk of developing cardiovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small (34). However, both studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mor- tality rate associated with different methods of contraception at different stages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s (33). Current clinical recommenda- tion involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although car- diovascular disease risk may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low- dose oral contraceptive use by healthy non-smoking women over 40 may out- weigh the possible risks.

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

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No fertility control methods</td>
<td>7.0</td>
<td>7.4</td>
<td>9.1</td>
<td>14.8</td>
<td>29.7</td>
<td>28.2</td>
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</tr>
<tr>
<td>Oral contraceptives non-smoker</td>
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<td>0.5</td>
<td>0.9</td>
<td>1.9</td>
<td>13.8</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives smoker**</td>
<td>2.2</td>
<td>3.4</td>
<td>6.8</td>
<td>13.5</td>
<td>31.1</td>
<td>117.2</td>
<td></td>
</tr>
<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></td>
<td>1.4</td>
</tr>
<tr>
<td>Condom</td>
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<td>1.6</td>
<td>0.7</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Diaphragm/spермидее</td>
<td>1.9</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Periodic sterility*</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>
<td></td>
</tr>
</tbody>
</table>

* Deaths are birth related ** Deaths are method related

(Adapted from H.R. K. Ory, ref. 95.)

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. While there are conflicting reports most studies suggest that the use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use (28-43, 79-89).
Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women (43-46). However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. HEPATIC NEOPLASIA

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

Studies from Britian have shown an increased risk of developing hepatocellular carcinoma (52-54) in long-term (5+ years) oral contraceptive users. However, these cancers are 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. GULLER LESIONS

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

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (56-57). The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned (58, 59) when oral contraceptives are taken inadvertently during early pregnancy.

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

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

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (60,61). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (52-54). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestagens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users (17). This effect has been shown to be directly related to estrone-sulfate (65). In general, progestagens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents (17, 66). In the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (67). Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistence hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1.3 and 1.6), 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 (68) and this increase is more likely in older oral contraceptive users (69) and with extended duration of use (71). Data from the Royal College of General Practitioners (12) and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease (70) should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptive should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives (69), and there is no difference in the occurrence of hypertension among former and never users (58,70,71).

10. HEADACHE

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

11. BLEEDING IRREGULARITIES

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

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

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW UP

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

2. LIPID DISORDERS

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

3. LIVER FUNCTION

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

4. FLUID RETENTION

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

5. EMOTIONAL DISORDERS

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

6. CONTACT LENSES

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

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampicin. A similar association, though less marked, has been suggested with barbiturates, phenytoin sodium, carbamazepine and possibly with phenacetin, aspirin and astatophenies (F2).

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX and X, decreased antithrombin
b. Increased homocysteine-induced platelet aggregability

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

d. Other binding proteins may be elevated in serum.

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

f. High-density lipoproteins (HDL-C) and triglycerides may be increased, while low-density lipoproteins cholesterol (LDL-C) and total cholesterol (Total-C) may be decreased or remain unchanged.

g. Glucose tolerance may be decreased.

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

9. CARDIOVASCULAR

See WARNINGS section.

10. PREGNANCY

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

11. NURSING MOTHERS

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

12. SEXUALLY TRANSMITTED DISEASES

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

INFORMATION FOR THE PATIENT

See Patient Labeling Printed Below

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section):

- Thromboembolism and various thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Salicylae disease
- Hepatic adenomas or benign liver tumors

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrintestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
Melasma which may persist
Breast changes: tenderness, enlargement, secretion
Change in weight (increase or decrease)
Change in cervix erosion and secretion
Dysmenorrhea in lactation when given immediately postpartum
Obstetric jaundice
Migraines
Rash (allergic)
Mental depression
Reduced tolerance to carbohydrates
Vaginal candidiasis
Change in core body temperature (fever, sweats)
Hypoalbuminemia
The following adverse reactions have been reported in users of oral contraceptives and
the association has been neither confirmed nor refuted:
- Nausea
- Cataracts
- Changes in appetite
- Ovary-like syndrome
- Breast tenderness
- Nausea
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Cystitis
- Budd-Chiari Syndrome

OVERDOSE
Serious side effects have not been reported following acute ingestion of large doses of oral
contraceptives by young women. Overdosage may cause nausea, and withdrawal
bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS
The following non-contraceptive health benefits related to the use of oral contraceptives
are supported by epidemiological studies which largely utilized oral contraceptive for-
mulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05
mg of mestranol (7S-7B):
Effects on menstruation:
- 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

DOSAGE AND ADMINISTRATION
To achieve maximum contraceptive effectiveness, April (desogestrel and ethinyl estradiol)
tablts must be taken exactly as directed and at intervals not exceeding 24 hours.
April tablets may be initiated using either a Sunday start or a Day 1 start.
NOTE. Each cycle pack blister card dispenser is preprinted with the days of the week,
starting with Sunday, to facilitate a Sunday start regimen. Six different "day label strips"
are provided with each cycle pack blister card in order to accommodate a Day 1 start
regimen. In this case, the patient should place the self-adhesive "day label strip" that
corresponds to her starting day over the preprinted days.

21-Day Regimen (Day 1 Start)
The dosage of the April Tablet 21-Day Regimen for the initial cycle of therapy is one tablet
administered daily from the 1st day through the 20th day of the menstrual cycle, count-
ing the first day of menstrual flow as "Day 1." For subsequent cycles, no tablets are
taken for 7 days, then a new course is started on one tablet a day for 21 days. The dosage
regimen then continues with 7 days of no medication, followed by 21 days of medicat-
on, instituting a three-weeks-on, one-week-off dosage regimen.
The use of the April Tablet 21-Day Regimen for contraception may be initiated 4 weeks
postpartum in women who do not lnot to breast feed. When the tablets are administered
during the postpartum period, the increased risk of thromboembolic disease associated
with the postpartum period must be considered. (See CONTRAINDICATIONS and
WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing
women. In one patient, the use of thiazides or other diuretics may cause metabolic alkalosis, and in another, the use of thiazides or other diuretics may cause hyperkalemia. In one patient, the use of thiazides or other diuretics may cause hypokalemia. In another patient, the use of thiazides or other diuretics may cause hyperkalemia. In yet another patient, the use of thiazides or other diuretics may cause hyperkalemia.

The use of the April tablet 21-Day regimen for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers"). If the patient starts on the April tablets postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a rose-colored tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day, and then continue taking one (1) tablet a day until she finishes the pack. If the patient misses two (2) active tablets in the third week or misses three (3) or more tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills. The patient should also be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills.

21-Day Regimen (Basal Start).

When using the April tablet 21-Day regimen, the first rose-colored tablet should be taken on the first Sunday after menstruation begins. If menstruation begins on Sunday, the first rose-colored tablet is taken on that day. If menstruation begins on another day, the first rose-colored tablet should be taken on the first Sunday after the last active tablet of the previous product. Rose-colored tablets are taken daily for 21 days. For subsequent cycles, no tablets are taken for seven days, then a new course is started of one tablet a day for 21 days. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills.

28-Day Regimen (Day 1 Start)
The dosage of the April tablet 28-Day regimen for the initial cycle of therapy is one tablet administered daily from the 1st day through 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1." Tablets are taken without interruption as follows: One rose-colored tablet daily for 21 days, then one white tablet daily for 7 days. After 28 tablets have been taken, a new course is started and a rose-colored tablet is taken the next day.

The use of the April tablet 28-Day regimen for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers"). If the patient starts on the April tablets postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a rose-colored tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day, and then continue taking one (1) tablet a day until she finishes the pack. If the patient misses two (2) active tablets in the third week or misses three (3) or more tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills.

28-Day Regimen (Basal Start).

When using the April tablet 28-Day regimen, the first rose-colored tablet should be taken on the first Sunday after menstruation begins. If menstruation begins on Sunday, the first rose-colored tablet is taken on that day. If switching directly from another oral contraceptive, the first rose-colored tablet should be taken on the first Sunday after the last active tablet of the previous product. One rose-colored tablet is taken daily for 21 days. For subsequent cycles, no tablets are taken for seven days, then a new course is started of one tablet a day for 21 days. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seventh (7) days after missing pills.

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

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

HOW SUPPLIED
Appl (dissolved in ethylool estradiol) Tabled 29 Day Regimen blister cards contain 21 round, uncoated tablets, 7 round, uncoated tablets that contain 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each round, uncoated tablet (dissolved with "A") on one side and "759" on the other side contains 0.24 mg desogestrel and 0.02 mg ethinyl estradiol. Each white tablet (dissolved with "B") on one side and "730" on the other side contains inert ingredients.


Appl (desogestrel and ethylool estradiol) Tabled 29 Day Regimen blister cards contain 21 round, uncoated tablets, 7 round, uncoated tablets that contain 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each round, uncoated tablet (dissolved with "B") on one side and "759" on the other side contains 0.24 mg desogestrel and 0.02 mg ethinyl estradiol.

Carnets of 6 blister cards NDC 51286-575-21.

STORAGE: Store at controlled room temperature 15°-30°C (59°-86°F).

B only

DURAMINE PHARMACEUTICALS, INC.
CONSUME, OHIO 44129 USA

REFERENCES
Brief Summary Patient Package Insert

Aprin
(desogestrel and ethinyl estradiol) Tablets

For women only.

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 about 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women, oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious illnesses that can be life-threatening or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly in those who:

- smoke
- have high blood pressure, diabetes, or high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or uterus, jaundice or a history of liver tumors

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

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

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (16 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

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

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

1. Blood clots in the legs (thrombophlebitis) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), or blockage of blood vessels in the heart and arteries caused by disease or injury (atherosclerosis). As mentioned above, smoking increases the risk of heart attack and stroke, and subsequent serious medical consequences.
2. Severe 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 rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

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

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

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

Be sure to discuss any medical condition you may have with your doctor or clinic. Your doctor or clinic 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 doctor or clinic believes that it is a good medical practice to postpone it. You should be examined at least once a year while taking oral contraceptives.

The detailed patient information labeling gives you further information which you should read and discuss with your doctor or clinic.
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.

**Detailed Patient Labeling**

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

The following oral contraceptive products contain a combination of progesterogen and estrogen, the two kinds of female hormones:

- Apt (desogestrel and ethinyl estradiol) Tablets 28 Day Regimen Blister Card
  Each rose-colored tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol.
  Each white tablet contains inert ingredients.

- Apt (desogestrel and ethinyl estradiol) Tablets 21 Day Regimen Blister Card
  Each rose-colored tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol.

**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 packet labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your doctor or clinic. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your reviews. You should also follow your doctor's or clinic'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 other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 users per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

- **Implant:** <1%
- **Injection:** 1% to 2%
- **IUD:** 1 to 2%
- **Diaphragm with spermicides:** 18%
- **Spermicides alone:** 21%
- **Vaginal sponge:** 18 to 36%
- **Cervical Cap:** 18 to 36%
- **Condom alone (male):** 12%
- **Condom alone (female):** 21%
- **Periodic abstinence:** 22%
- **No methods:** 85%

**Who Should Not Take Oral Contraceptives**

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

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

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

Tell your doctor or clinic if you have ever had any of these conditions. Your doctor or clinic can recommend a safer method of birth control.

**Other Considerations Before Taking Oral Contraceptives**

Tell your doctor or clinic if you have or have had:

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

Women with any of these conditions should be checked often by their doctor or clinic if they choose to use oral contraceptives. Also, be sure to inform your doctor or clinic if you smoke or are on any medications.

**Risks of Taking Oral Contraceptives**

1. Risk of developing blood clots. Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in one of the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blockage of the vessel carrying blood to the lungs. These risks are greater with desogestrel-containing oral contraceptives, such as Apt (desogestrel and ethinyl estradiol) tablets, than with other low-dose pills. Rarely, clots occur in the blood vessels of the eyes and may cause blindness, double vision, or impaired vision.

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

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

2. Heart attack and strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attack (stoppage 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.


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

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 cancer 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 rare.

5. Cancer of the reproductive organs and breasts

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

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

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

<table>
<thead>
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<td>UD**</td>
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<td>1.0</td>
<td>1.0</td>
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<td>1.7</td>
<td>2.9</td>
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</tr>
</tbody>
</table>

* Deaths are birth related

** Deaths are method related

In the preceding 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 36, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was almost as low as that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 29 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 (29/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed the issue in 1995 and recommended that the use of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor or clinic 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 lump (indicating possible breast cancer or fibrocystic disease of the breast, ask your doctor or clinic to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or whites of the eyes, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or hight colored bowel movements (indicating possible liver problems)
SIDE EFFECTS OF ORAL CONTRACEPTIVES

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

2. Contact lenses
   If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or clinic.

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

4. Menstrual
   A heavy or bleeding may be possible, particularly of the face, which may persist.

5. Other side effects
   Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, acne, discomfort, loss of scalp hair, mood, and vaginal infections. If any of these side effects bother you, call your doctor or clinic.

GENERAL PRECAUTIONS

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

2. High breast feeding
   If you are breast feeding, consult your doctor or clinic before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse reactions on the child have been reported, including yellowing 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 your 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 or clinic 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 tranquilizers, drugs used for epilepsy, such as Dilantin (for example), phenobarbital, antibiotics such as tetracycline, aspirin, drugs used to treat gout, and phenothrin (Dieldrin is one brand of this drug), phencyclidine (Butisol is one brand), and possibly certain antibiotics. You may need to use additional contraception when you use these drugs which can make oral contraceptives less effective.

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 THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS

1. BE SURE TO READ THESE DIRECTIONS
   Before you start taking your pills, any time 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 setting the pack aside. The more pills you miss, the more likely you are to get pregnant.

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

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

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or if you take some MEDICATIONS, including some antibiotics, your pills may not work as well.
   Use a backup method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

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

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

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILLS, IT IS IMPORTANT TO
If at about the same time every day:

2. LOOK AT YOUR Pill PACK TO SEE IF IT HAS 21 OR 28 PILLS:
The 21-pill pack has 21 "active" (rose-colored) pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The 28-pill pack has 21 "active" (rose-colored) pills (with hormones) to take for 3 weeks, followed by 1 week of "no pills" (without hormones).

3. ALSO READ:
1) where on the pack to start taking the pills,
2) in what order to take the pills (follow the arrows) and
3) the week numbers printed on the pack.

28 Pill Pack

3. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up 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 doctor or clinic which is the best day for you. Pick a day of the month which will be easy to remember.

DAY 1 START:
1. Pick the day label strip that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)
2. Place this day label strip on the cycle label dispenser over the area that has the date of the week (Monday through Sunday) printed on the blister card.

Pick Correct Day Label

Note: If the first day of your period is a Sunday, you can also start on Monday.

4. Take the first "active" (rose-colored) pill of the first pack during the first 24 hours of your period.

5. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

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 periods or feel sick to your stomach (nausea).
2. Do not skip pills if you do not have sex very often.

2. WHEN YOU RUN OUT OF PILLS OR SWITCH YOUR BRAND OF PILLS:

21 pills:
Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.

28 pills:
Start the next pack on the day after your last "remind" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS:
If you MISS 1 (rose-colored) "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
2. Do not need to use a back-up birth control method if you have sex.

If you MISS 2 (rose-colored) "active" pills in a row in WEEK 1 OR WEEK 2 of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 4 days after you miss pills. You MUST use another back-up birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

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

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you take any of the 1 (white) "reminder" pills in Week 4, THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING THE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

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

PREGNANCY AFTER STOPPING THE PILLS:
There may be some delay in becoming pregnant after you stop taking contraceptive pills. If you have irregular menstrual cycles before you used oral contraceptives, it may be advisable to postpone conception until you begin menstruating regularly again after you have stopped taking the pill and desiring pregnancy.

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

OVERDOSE:
Serious side effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdose may cause nausea and withdrawal bleeding in females. In case of overdose, contact your doctor, clinic or pharmacist.

OTHER INFORMATION:
Your doctor or clinic 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 doctor or clinic believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your doctor or clinic if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your doctor or clinic because this is a time to determine if there are early signs of side effects of oral contraceptive use.

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

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:
In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular.
- Irregular bleeding during menstruation may be lighter and less iron may be lost. Therefore, anemia due to an iron deficiency is less likely to occur.
- Nausea or other symptoms during menstruation may be encountered less frequently.
- Nonspecific (noninfectious) menstrual cramps may occur less frequently.
- Menstrual cramps due to the progestin in the pill may occur less frequently.
- Certain pelvic inflammatory disease may occur less frequently.
- Women who use oral contraceptives may have some protection against developing two forms of cancer: cancer of the ovary and cancer of the lining of the uterus.

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

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45213 USA
Brief Summary Patient Instruction

April

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

Monday: MON
Tuesday: TUE
Wednesday: WED
Thursday: THU
Friday: FRI
Saturday: SAT
Sunday: SUN

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

April (desogestrel and ethinyl estradiol) Tablet 21 Day Regimen blister pack contains 21 round rose-colored tablets in a blister card attached to a "credit card" dispenser. Each rose-colored tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol.

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. The risks associated with taking oral contraceptives increase significantly if you:

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

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

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

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (10 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bloating between menstrual periods, weight gain, breast tenderness, headaches, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first
three months of use. The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis) or lungs (pulmonary embolism), stroke or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attack and stroke, and subsequent serious medical consequences.
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 patient labeling given to you with your supply of pills. Notify your doctor or clinic if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as antihypertensives, as well as some antibiotics and some antibiotics may decrease oral contraceptive effectiveness.

There is little evidence of any increased risk of developing breast cancer, particularly in the younger age group. However, studies have suggested an increase in the risk of developing breast cancer in women who use oral contraceptives. However, this finding may be related to other factors rather than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the pill provides some important non-contraceptive benefits. These include less painful menstruation, less menopausal bleeding and menorrhagia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Before you start taking any medical condition you may have with your doctor or clinic, your doctor or clinic 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 doctor believes that is a good medical practice to postpone it. You should be reassured at least once a year while taking oral contraceptives. The detailed patient labeling gives you further information which you should read and discuss with your doctor or clinic.

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, GONORRHEA, CHLAMYDIA TYPHIMURIUM, HEPATITIS B, AND SYphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER:

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS.
   Before you start taking your pills,
   anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILLS IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME. If you miss a pill, you may get pregnant. This includes taking the first pill on the pack. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE AVOIDING OR DIARRHEA, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 DAYS OF PILLS. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away.
4. IF YOU HAVE VOMITING OR DIARRHEA, FOR ANY REASON. If you take these missed pills. On the days you take 2 pills to make up for missed pills, you should also take a little sick to your stomach.
5. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make it easier or about using another method of birth control.
6. IF YOU HAVE ANY QUESTIONS OR ARE UNCERTAIN ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS:
1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE THAT IT HAS 21 PILLS. The 21-pill pack has 21 "active" (progesterone) pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
3. ALSO FUND:
   1. where on the pack to start taking the pills,
   2. in what order to take the pills (follow the arrows), and
   3. the week numbers as shown in the following example:

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

WHEN TO START THE ORIGIN PACK OF PILLS:
You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SAFETY STOPS:
1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip on the cycle tablet dispenser card over the area that has the days of the week (starting with Sunday) printed on the dispensing card.

Pick correct day label
THU FRI SAT SUN MON TUE WED

Peel and place label here.

Example
Only:
Note: If the first day of your period is on a Sunday, you can skip days 1 and 2.

3. Take the first "active" tablet of the first pack during the first 2 days of your period.
4. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

WHAT TO DO DURING THE MONTH:
1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
   Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
   Do not skip pills even if you do not have sex very often.
2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
   Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.

WHAT TO DO IF YOU MISS PILL:
If you Miss 1 (rose-colored) "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you take
   2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you Miss 2 (rose-colored) "active" pills in a row in WEEK 1 OR WEEK 2 of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 2 days after you miss pills.
   You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 2 days.
If you Miss 3 (rose-colored) "active" pill in a row in the 3rd WEEK:
1. If you are a Day 3 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.
   If you may not have your period this month but this is expected, however, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
   You MAY BECOME PREGNANT if you have sex in the 2 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 3 days.
If you Miss 3 OR MORE (rose-colored) "active" pills in a row (during the first 3 weeks):
1. If you are a Day 3 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.
   You may not have your period this month but this is expected, however, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
   You MAY BECOME PREGNANT if you have sex in the 2 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE (ROSE-COLORED) "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

GURNEY PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45219 USA
1983208
REV. 05/88
Apri™
(desogestrel and ethinyl estradiol) Tablets

6 Cyclic Tablet Dispensers x 28 Tablets
NDC 51285-576-20

28 DAY REGIME

0.15mg/0.03mg

ethinyl estradiol (Tables)
desogestrel and
Apri™
(desogestrel and ethinyl estradiol) Tablets

0.15mg/0.03mg

21 DAY REGIMEN
B only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

If unsure or if bleeding continues, consult your physician.

Contains: One cyclic tablet dispenser of 21 tablets.
Apri™
(desogestrel and ethinyl estradiol) Tablets

0.15mg/0.03mg

28 DAY REGIMEN

B only

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

Contents: One cyclic tablet dispenser x 28 tablets

DURAMED PHARMACEUTICALS INC.
CINCINNATI, OHIO 45215 USA
**DETAILED PATIENT LABELING**

**April**
(desogestrel and ethinyl estradiol) Tablets

**28 and 21 Day Regimens**

**THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.**

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

The following oral contraceptive products contain a combination of progestogen and estrogen, the two kinds of female hormones:

- **April (desogestrel and ethinyl estradiol) Tablet 28 Day Regimen Blister Card**
  Each rose-colored tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each white tablet contains inert ingredients.

- **April (desogestrel and ethinyl estradiol) Tablet 21 Day Regimen Blister Card**
  Each rose-colored tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol.

**INTRODUCTION**

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

- You should also follow your doctor's or clinic's advice with regard to regu-
  lar check-ups while you are on the pill.

**EFFECTIVENESS OF ORAL CONTRACEPTIVES**

Oral contraceptives are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women year of use) when used perfectly, with no missed any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

- **Implant:** <1%
- **Injection:** <1%
- **IUD:** 1 to 2%
- **Diaphragm with spermicides:** 18%
- **Spermicides alone:** 21%
- **Vaginal sponge:** 18 to 26%

**to the lungs. These risks are great with desogestrel-containing oral contraceptives, such as April (desogestrel and ethinyl estradiol) tablets, than with other low-dose pills. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.**

If you take oral contraceptives and need elective surgery, you should stay in bed for at least 24 hours after surgery. If you have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor or clinic 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. It is advisable to wait for at least four weeks after delivery if you are not breastfeeding your child for at least two months after delivery. If you are breastfeeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in General Precautions.)

The risk of circulatory disease in oral contraceptives may be higher in users of high dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risk may continue for at least two years after stopping oral contraceptives. The risk of abnormal bleeding complications increases with age and oral contraceptives are contraindicated in women who have had a stroke. Among non-users in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 24 the risk of death due to a circul-

**WARNING SIGNALS**

- 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, dizzy 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 lump (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or clinic to show you how to examine your breasts)
- Severe or tenderness in the stomach area (indicating possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, loss of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyes (possibly accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems))

**SIDE EFFECTS OF ORAL CONTRACEPTIVES**

1. **Vaginal bleeding**
   - Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious prob-
WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

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

Some women should not use the pill for the following conditions:

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

Tell your doctor or clinic if you have ever had any of these conditions. Your doctor or clinic can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your doctor or clinic if you have any of the following conditions. Your doctor or clinic may recommend that you take oral contraceptives:

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

Women with any of these conditions should be checked often by your doctor or clinic if they choose to use oral contraceptives. Also, be sure to inform your doctor or clinic if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in one of the legs can cause a sudden blocking of the vessel carrying blood to the lungs can cause a sudden death. 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 rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are rare.

2. Cancer of the reproductive organs and breasts

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

3. 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 birth control methods and pregnancy has been calculated and is shown in the following table.

<table>
<thead>
<tr>
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</thead>
<tbody>
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<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Oral contraceptives non-smoker**</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Oral contraceptives smoker**</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>1.0</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>IUD**</td>
<td>0.8</td>
<td>1.1</td>
<td>1.3</td>
<td>1.6</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Condom*</td>
<td>1.6</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Diaphragm/permacide*</td>
<td>1.2</td>
<td>1.5</td>
<td>1.8</td>
<td>2.2</td>
<td>2.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Oral contraceptive with pregnancy*</td>
<td>1.0</td>
<td>1.2</td>
<td>1.5</td>
<td>1.8</td>
<td>2.1</td>
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</tr>
</tbody>
</table>

* Deaths are birth related

In the previous table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptives used by 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 (7-28 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are

4. Menstrual irregularities

If you experience menstrual irregularities, your doctor or clinic may recommend that you take oral contraceptives.

5. Other side effects

Other side effects may include nausea and vomiting, change in appetite, headaches, nervousness, depression,碉石ness, loss of scalp hair, rash, and vaginal infections. If any of these side effects bother you, call your doctor or clinic.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy

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

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

2. While breast feeding

If you are breast feeding, consult your doctor or clinic before stopping oral contraceptives. Some of the drugs will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, 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 or clinic if you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. Drug interactions

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

5. Sexually transmitted diseases

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 THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:

   Before you start taking your pills. Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT

   THE SAME TIME.

   If you miss pills you could get pregnant. This includes starting the pack late.

   The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK

   TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.

   If you feel sick to your stomach, do not stop taking the pill. The problem will

   usually go away. If it doesn’t go away, check with your doctor or clinic.

4. MISSED PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even

   when you make up these missed pills. On the days you take 2 pills to make

   up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or if YOU TAKE

   SOME MEDICINES, including some antibiotics, your pills may not work as

   well.

   Use a back-up method (such as condoms, foam, or sponge) until you check

   with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your

   doctor or clinic about how to make pill-taking easier or about using another

   method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION

   IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS:

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL, it is impor-

   tant to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:

   The 21-pill pack has 21 “active” [rose-colored] pills (with hormones) to take

   for 3 weeks, followed by 1 week without pills.

   The 28-pill pack has 21 “active” [rose-colored] pills (with hormones) to take

   for 3 weeks, followed by 1 week of reminder [white] pills (without hor-

   mones).

3. ALSO FIND:

   1) where on the pack to start taking the pills,

   2) in what order to take the pills (follow the arrows) and

   3) the week numbers printed on the pack.

SUNDAY START:

1. Take the first “active” [rose-colored] 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 on that day.

2. Use a back-up method of birth control as a back-up method if you have sex

   anytime throughout the Sunday you start your first pack until the next Sunday (7

   days). Condoms, foam, or the sponge are good back-up methods of birth

   control.

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 peri-

   ods or feel sick to your stomach (nausea).

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

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:

   21 pills: Wait 7 days to start the next pack. You will probably have your

   period during that week. Be sure that no more than 7 days pass

   between 21-day packs.

   28 pills: Start the next pack on the day after your last “reminder” pill. Do

   not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS:

If you MISS 1 [rose-colored] “active” pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This

   means you take 2 pills in 1 day.

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

   If you MISS 2 [rose-colored] “active” pills in a row in WEEK 1 OR

   WEEK 2 of your pack:

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

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

   3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss

      pills. You MUST use another birth control method (such as condoms, foam,

      or sponge) as a back-up method for those 7 days.

   If you MISS 2 [rose-colored] “active” pills in a row in WEEK 3:

   1. If you are a Day 1 Starter:

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

   2. 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 doctor or clinic because

      you might be pregnant.

   3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss

      pills. You MUST use another birth control method (such as condoms, foam,

      or sponge) as a back-up method for those 7 days.

   If you MISS 3 OR MORE [rose-colored] “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.

   2. 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 doctor or clinic because

      you might be pregnant.

   3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss

      pills. You MUST use another birth control method (such as condoms, foam,

      or sponge) as a back-up method for those 7 days.
4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge)
to use as a back-up 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 doctor or clinic which is the best day for you. Pick a time of day
which will be easy to remember.

DAY 1 STARTS:
1. Pick the day label strip that starts with the first day of your period (this is
the day you start bleeding or spotting, even if it is almost midnight when the
bleeding begins.)
2. Place this day label strip in the cycle tablet dispenser over the area that has
the days of the week (starting with Sunday) printed on the blister card.

Pick Correct Day Label

Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.
3. Take the first “active” [rose-colored] pill of the first pack during the first 24
hours of your period.
4. You will not need to use a back-up method of birth control, since you are
starting the pill at the beginning of your period.

A REMINDER FOR THOSE ON 28 DAY PACKS:
If you forget any of the 7 [white] “reminder” pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU
HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE [rose-colored] “ACTIVE” PILL EACH DAY until you can
reach your doctor or clinic.

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

PREGNANCY AFTER STOPPING THE PILL
There may be some delay in becoming pregnant after you stop using oral con-
traceptives, 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 preg-
nancy.
There does not appear to be any increase in birth defects in newborn babies
when pregnancy occurs soon after stopping the pill.

OVERDOSE
Serious side effects have not been reported following ingestion of large doses of
oral contraceptives by young children. Overdosage may cause nausea and
withdrawal bleeding in females. In case of overdosage, contact your doctor,
clinics or pharmacists.

OTHER INFORMATION
Your doctor or clinic 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 doctor or clinic believes that
it is a good medical practice to postpone it. You should be reexamined at least
once a year. Be sure to inform your doctor or clinic if there is a family history
of any of the conditions listed previously in this leaflet. Be sure to keep all
appointments with your doctor or clinic 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 pre-
scribed. This drug has been prescribed specifically for you; do not give it to
others who may want birth control pills.

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

If you want more information about birth-control pills, ask your doctor, clinic or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The Professional Labeling is also published in a book entitled Physicians' Desk Reference, available in most bookstores and public libraries.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45213 USA

100391A REV 06/90
0.15mg/0.03mg

IMPORTANT:
This package contains Detailed Patient Labeling and each blister pack. Minor or adjunctive indication(s) should be included with each package dispensed in the package.

PHARMACIST:
Please be sure to place one of the enclosed "instructions" stickers on the cover of each blister card prior to the time of dispensing.

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

B only