DESOGEN® Tablets

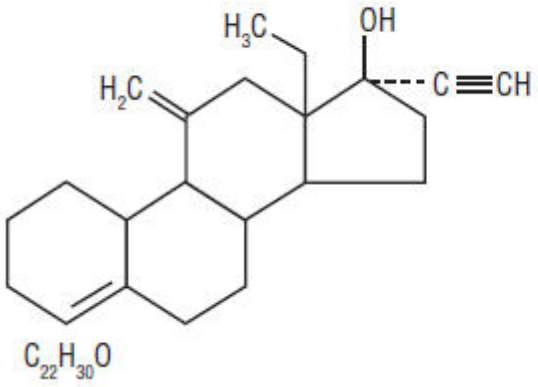
(desogestrel and ethinyl estradiol tablets USP)

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

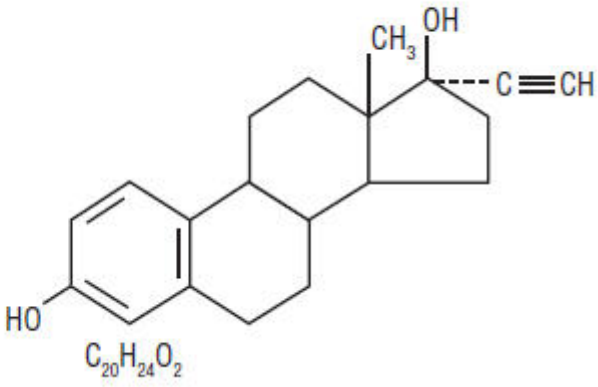
DESCRIPTION

DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) provides an oral contraceptive regimen of 21 white round tablets each containing 0.15 mg desogestrel (13-ethyl-11-methylene-18,19-dinor-17 alpha-pregn-4-en-20-yn-17-ol) and 0.03 mg ethinyl estradiol (19-nor-17 alpha-pregna-1,3,5 (10)-trien-20-yne-3,17-diol). Inactive ingredients include vitamin E, corn starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc. DESOGEN® also contains 7 green round tablets containing the following inert ingredients: lactose, corn starch, magnesium stearate, FD&C Blue No. 2 aluminum lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc. The molecular weights for desogestrel and ethinyl estradiol are 310.48 and 296.40, respectively. The structural formulas are as follows:

DESOGESTREL



ETHINYL ESTRADIOL



CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor-binding studies, as well as studies in animals, have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity (91,92). The relevance of this latter finding in humans is unknown.

Pharmacokinetics

Absorption

Desogestrel is rapidly and almost completely absorbed and converted into etonogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of etonogestrel, is approximately 84%.

In the third cycle of use after a single dose of DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP), maximum concentrations of etonogestrel of 2805±1203 pg/mL (mean±SD) are reached at 1.4±0.8 hours. The area under the curve ($AUC_{0-\infty}$) is 33,858±11,043 pg/mL•hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of 5840±1667 pg/mL are reached at 1.4±0.9 hours. The minimum plasma levels of etonogestrel at steady state are 1400±560 pg/mL. The AUC_{0-24} at steady state is 52,299±17,878 pg/mL•hr. The mean $AUC_{0-\infty}$ for etonogestrel at single dose is significantly lower than the mean AUC_{0-24} at steady state. This indicates that the kinetics of etonogestrel are non-linear due to an increase in binding of etonogestrel to SHBG in the cycle, attributed to increased SHBG levels which are induced by the daily administration of ethinyl estradiol. SHBG levels increased significantly in the third treatment cycle from day 1 (150±64 nmol/L) to day 21 (230±59 nmol/L).

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single dose of DESOGEN®, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of DESOGEN®, maximum concentrations of ethinyl estradiol of 95±34 pg/mL are reached at 1.5±0.8 hours. The $AUC_{0-\infty}$ is 1471±268 pg/mL•hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of 141±48 pg/mL are reached at about 1.4±0.7 hours. The minimum serum levels of ethinyl estradiol at steady state are 24±8.3 pg/mL. The AUC_{0-24}, at steady state is 1117±302 pg/mL•hr. The mean $AUC_{0-\infty}$ for ethinyl estradiol following a single dose during treatment cycle 3 does not significantly differ from the mean AUC_{0-24} at steady state. This finding indicates linear kinetics for ethinyl estradiol.

Distribution

Etonogestrel, the active metabolite of desogestrel, was found to be 98% protein bound, primarily to sex hormone-binding globulin (SHBG). Ethinyl estradiol is primarily bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone (96–99).

Metabolism

Desogestrel: Desogestrel is rapidly and completely metabolized by hydroxylation in the intestinal mucosa and on first pass through the liver to etonogestrel. *In vitro* data suggest an important role for the cytochrome P450 CYP2C9 in the bioactivation of desogestrel. Further metabolism of etonogestrel into 6β-hydroxy, etonogestrel and 6β-13ethyl-dihydroxylated metabolites as major metabolites is catalyzed by CYP3A4. Other metabolites (i.e., 3α-OHdesogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel)

also have been identified and these metabolites may undergo glucuronide and sulfate conjugation.

Ethinyl estradiol: Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol, escaping gut wall conjugation, undergoes phase I 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.

Excretion
Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces. The elimination half-life of etonogestrel is approximately 38±20 hours at steady state. The elimination half-life of ethinyl estradiol is 26±6.8 hours at steady state.

Special Populations

Race
There is no information to determine the effect of race on the pharmacokinetics of DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP).

Hepatic Insufficiency
No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of DESOGEN®. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

Renal Insufficiency
No formal studies were conducted to evaluate the effect of renal disease on the disposition of DESOGEN®.

Drug–Drug Interactions
Interactions between desogestrel/ethinyl estradiol and other drugs have been reported in the literature. No formal drug-drug interaction studies were conducted with DESOGEN® (see PRECAUTIONS).

INDICATIONS AND USAGE

DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. **Table 1** lists the typical unintended pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, the IUD, and implants, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

TABLE 1: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY

DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR: UNITED STATES.

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year* (4)
	Typical Use† (2)	Perfect Use‡ (3)	
Chance§	85	85	
Spermicides¶	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal#		2	
Post-Ovulation		1	
Withdrawal	19	4	
Capþ			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragmþ	20	6	56
Condomß			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces risk of pregnancy by at least 75%.à

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.è

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

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

† Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

‡ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

§ The percentage of women becoming pregnant noted in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% became pregnant in one year. This estimate was lowered slightly (to 85%) to represent the percentage that would become pregnant within one year among women now relying on reversible methods of contraception if they abandon contraception altogether

¶ Foams, creams, gels, vaginal suppositories and vaginal film

[#] Cervical mucous (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases

[þ] With spermicidal cream or jelly

[ß] Without spermicides

[à] The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral® (1 dose is 2 white pills), Alesse®(1 dose is 5 pink pills), Nordette® or Levlen® (1 dose is 2 light orange pills), Lo/Ovral® (1 dose is 4 white pills), Triphasil® or Tri-Levlen® (1 dose is 4 yellow pills)

[è] However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast-feeds is reduced, bottle feeds are introduced or the baby reaches six months of age

CONTRAINDICATIONS

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

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease (current or history)
- Valvular heart disease with thrombogenic complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast (or personal history of breast cancer)
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Hepatic tumors (benign or malignant) or active liver disease
- Known or suspected pregnancy
- Heavy smoking (≥15 cigarettes per day) and over age 35
- Hypersensitivity to any of the components of DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP)

WARNINGS

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

The use of oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as

certain inherited thrombophilias, hypertension, hyperlipidemias, obesity, and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens 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 progestogens remains to be determined.

Throughout this labeling, epidemiologic 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 non-users. 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 non-users. The attributable risk does provide information about the actual occurrence of a disease in the population (Adapted from refs. 2 and 3 with the authors' permission). For further information, the reader is referred to a text on epidemiologic methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to 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).

Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives (102–104). In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1–2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk.

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives (9,26). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (9,26). If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two

weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breast-feed.

b. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (4–10). The risk is very low 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 infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases (11). Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 (**Table 2**) among women who use oral contraceptives.

TABLE 2: CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN-YEARS BY AGE, SMOKING STATUS, AND ORAL CONTRACEPTIVE USE.

AGE	EVER-USERS NON-SMOKERS	EVER-USERS SMOKERS	CONTROLS NON-SMOKERS	CONTROLS SMOKERS
15–24	0.0	10.5	0.0	0.0
25–34	4.4	14.2	2.7	4.2
35–44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

Adapted from P.M. Layde and V. Beral, ref. #12.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity (13). In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (14–18). Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

c. Cerebrovascular diseases

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

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension (30). The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension (30). The attributable risk is also greater in older women (3). Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

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

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

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

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 other age groups (8). In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small (34). However, both studies were performed with oral contraceptive formulations containing 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 mortality rate associated with different methods of contraception at different ages

(**Table 3**). 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 a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's – but not reported until 1983 (35). However, current clinical practice involves the use of lower estrogen formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed (103,104), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 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.

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

TABLE 3: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE.

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth related

†Deaths are method related

Adapted from H.W. Ory, ref. #35.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiologic studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives.

Although the risk of breast cancer may be slightly increased among current users of oral contraceptives (RR = 1.24), this excess risk decreases over time after oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less advanced clinically than in never-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intra-epithelial neoplasia in some populations of women (45–48). However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of 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 rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage (50,51).

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma (52–54) in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been 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 epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (55–57). Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and

limb reduction defects are concerned (55,56,58,59), 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. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (60,61). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (62–64). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users (17). Oral contraceptives containing greater than 75 micrograms of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance (65). Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents (17,66). However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (67). Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1.a. and 1.d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

Women with severe hypertension should not be started on hormonal contraceptives. 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 continued use (61). Data from the Royal College of General Practitioners (12) and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease (70) should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives (69), and there is no difference in the occurrence of hypertension between ever- and never-users (68,70,71).

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. If bleeding persists or recurs, non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

12. ECTOPIC PREGNANCY

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

PRECAUTIONS

1. SEXUALLY TRANSMITTED DISEASES

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

2. PHYSICAL EXAMINATION AND FOLLOW UP

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

3. 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.

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

4. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. The hormones in DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) may be poorly metabolized in patients with impaired liver function.

5. FLUID RETENTION

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

6. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. CONTACT LENSES

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

8. DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other drugs:

a. Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with some antibiotics, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and griseofulvin.

Since desogestrel is mainly metabolized by the cytochrome P450 2C9 enzyme (CYP 2C9) to form etonogestrel, the active progestin, there is a possibility of interaction with CYP 2C9 substrates or inhibitors (such as: ibuprofen, piroxicam, naproxen, phenytoin, fluconazole, diclofenac, tolbutamide, glipizide, celecoxib, sulfamethoxazole, isoniazid, torsemide, irbesartan, losartan, and valsartan). The clinical relevance of these interactions is unknown.

b. Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The efficacy and safety of these oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers

should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. Herbal products

Herbal products containing St. John's wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma hormone levels associated with co-administered drugs:
Co-administration of atorvastatin and certain ethinyl estradiol containing oral contraceptives increased AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs:
Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid, have been noted when these drugs were administered with oral contraceptives.

No formal drug-drug interaction studies were conducted with DESOGEN®.

9. INTERACTIONS WITH LABORATORY TESTS

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

a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

10. CARCINOGENESIS

See WARNINGS section.

11. PREGNANCY

Pregnancy Category X (see CONTRAINDICATIONS and WARNINGS sections).

12. NURSING MOTHERS

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

13. PEDIATRIC USE

Safety and efficacy of DESOGEN® has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

14. GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

INFORMATION FOR THE PATIENT

See Patient Labeling Printed Below

ADVERSE REACTIONS

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

- Thrombophlebitis and venous thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives:

- Mesenteric thrombosis
- Retinal thrombosis

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

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal pain, cramps and bloating)
- Change in weight or appetite (increase or decrease)
- Change in cervical ectropion and secretion
- Possible diminution in lactation when

- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema/fluid retention
- Melasma/chloasma which may persist
- Breast changes: tenderness, pain, enlargement, and secretion
- Decrease in serum folate levels
- Exacerbation of porphyria
- Aggravation of varicose veins
- given immediately postpartum
- Cholestatic jaundice
- Migraine headache
- Rash (allergic)
- Mood changes, including depression
- Vaginitis, including candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses
- Exacerbation of systemic lupus erythematosus
- Exacerbation of chorea
- Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Cataracts
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Dysmenorrhea
- Pancreatitis
- Erythema nodosum
- Hemorrhagic eruption
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome
- Optic neuritis, which may lead to partial or complete loss of vision

OVERDOSAGE

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

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiologic studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol (73–78).

Effects on menses:

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia

- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

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, DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) must be taken exactly as directed, at the same time every day, and at intervals not exceeding 24 hours. DESOGEN® may be initiated using either a Sunday start or a Day 1 start.

NOTE: Seven different "day label strips" are provided to accommodate the selected start regimen. The patient should place the self-adhesive "day label strip" that corresponds to her starting day on the blister card above the first row of tablets.

DURING THE FIRST CYCLE OF USE:

IMPORTANT: The possibility of ovulation and conception prior to initiation of use of DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) should be considered. A woman can begin to take DESOGEN® either on the first Sunday after the onset of her menstrual period (Sunday Start) or on the first day of her menstrual period (Day 1 Start). When switching from another oral contraceptive, DESOGEN® should be started on the same day that a new pack of the previous oral contraceptive would have been started.

SUNDAY START

When initiating a Sunday start regimen, another method of contraception, such as condoms or spermicide, should be used for the first 7 consecutive days of taking DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP).

Using a Sunday start, tablets are taken daily without interruption as follows: The first white tablet should be taken on the first Sunday after menstruation begins (if menstruation begins on Sunday, the first white tablet is taken on that day). Tablets are then taken sequentially following the arrows marked on the blister card. One white tablet is taken daily for 21 days, followed by 1 green (inactive) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28-tablet regimen on the next day (Sunday) after taking the last green (inactive) tablet. [If switching from a different Sunday Start oral contraceptive, the first DESOGEN® tablet should be taken on the same day that a new pack of the previous oral contraceptive would have been started.]

If a patient misses 1 white (active) tablet in Weeks 1, 2, or 3, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive white tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control (such as condoms or spermicide) if she has intercourse in the 7 days after she restarts her pills. If the patient misses 2 consecutive white tablets in the third week or misses 3 or more white tablets in a row at any time during the cycle, the patient should keep taking 1 white tablet daily until the next Sunday. On Sunday the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after restarting her pills.

Complete instructions to facilitate patient counseling on proper pill usage can be found in Detailed or Brief Patient Labeling ("How to Take the Pill" section).

DAY 1 START

Counting the first day of menstruation as "Day 1", the first white tablet should be taken on the first day of menstrual bleeding. Tablets are then taken sequentially without interruption as follows: One white tablet daily for 21 days, then one green (inactive) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28-tablet regimen on the next day after taking the last green (inactive) tablet. [If switching directly from another oral contraceptive, the first white tablet should be taken on the same day that a new pack of the previous oral contraceptive would have been started.]

If a patient misses 1 white tablet, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive white tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control (such as condoms or spermicide) if she has intercourse in the 7 days after she restarts her pills. If the patient misses 2 consecutive white tablets in the third week or misses 3 or more white tablets in a row at any time during the cycle, the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after restarting her pills.

Complete instructions to facilitate patient counseling on proper pill usage can be found in Detailed or Brief Patient Labeling ("How to Take the Pill" section).

ADDITIONAL INSTRUCTIONS FOR BOTH SUNDAY AND DAY 1 STARTS

If Spotting or Breakthrough Bleeding Occurs

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-functional causes should be considered. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If both pregnancy and pathology have been excluded, time or a change to another preparation 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 DESOGEN® 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 DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) use should be discontinued if pregnancy is confirmed.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. DESOGEN® should be discontinued if pregnancy is confirmed.

Use of DESOGEN® Postpartum

The use of DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) for contraception may be initiated 4 to 6 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 DESOGEN® postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a white tablet has been taken daily for 7 consecutive days.

HOW SUPPLIED

DESOGEN® Tablets (desogestrel and ethinyl estradiol tablets USP) contains 21 round white tablets and 7 round green tablets in a blister card. Each white tablet (debossed with "$^{T}_{5}{}^{R}$" on one side and "Organon" on the other side) contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each green tablet (debossed with "$^{K}_{2}{}^{H}$" on one side and "Organon" on the other side) contains inert ingredients.

Box of 6	NDC 0052-0261-06
Box of 1	NDC 0052-0261-08

Storage: Store below 30°C (86°F).

Rx only

REFERENCES

1. Hatcher RA, Trussell J, Stewart F et al. Contraceptive Technology: Seventeenth Revised Edition, New York: Irvington Publishers, 1998. **2.** Stadel BV. Oral contraceptives and cardiovascular disease. (Pt. 1). N Engl J Med 1981; 305:612–618. **3.** Stadel BV. Oral contraceptives and cardiovascular disease. (Pt. 2). N Engl J Med 1981; 305:672–677. **4.** Adam SA, Thorogood M. Oral contraception and myocardial infarction revisited: the effects of new preparations and prescribing patterns. Br J Obstet and

Gynecol 1981; 88:838–845. **5.** Mann JI, Inman WH. Oral contraceptives and death from myocardial infarction. Br Med J 1975; 2(5965):245–248. **6.** Mann JI, Vessey MP, Thorogood M, Doll R. Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 1975; 2(5956):241–245. **7.** Royal College of General Practitioners' Oral Contraception Study: Further analyses of mortality in oral contraceptive users. Lancet 1981; 1:541–546. **8.** Slone D, Shapiro S, Kaufman DW, Rosenberg L, Miettinen OS, Stolley PD. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. N Engl J Med 1981; 305:420–424. **9.** Vessey MP. Female hormones and vascular disease–an epidemiological overview. Br J Fam Plann 1980; 6:1–12. **10.** Russell-Briefel RG, Ezzati TM, Fulwood R, Perlman JA, Murphy RS. Cardiovascular risk status and oral contraceptive use, United States, 1976–80. Prevent Med 1986; 15:352–362. **11.** Goldbaum GM, Kendrick JS, Hogelin GC, Gentry EM. The relative impact of smoking and oral contraceptive use on women in the United States. JAMA 1987; 258:1339–1342. **12.** Layde PM, Beral V. Further analyses of mortality in oral contraceptive users: Royal College General Practitioners' Oral Contraception Study. (Table 5) Lancet 1981; 1:541–546. **13.** Knopp RH. Arteriosclerosis risk: the roles of oral contraceptives and postmenopausal estrogens. J Reprod Med 1986; 31(9) (Supplement):913–921. **14.** Krauss RM, Roy S, Mishell DR, Casagrande J, Pike MC. Effects of two low-dose oral contraceptives on serum lipids and lipoproteins: Differential changes in high-density lipoproteins subclasses. Am J Obstet 1983; 145:446–452. **15.** Wahl P,Walden C, Knopp R, Hoover J, Wallace R, Heiss G, Rifkind B. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. N Engl J Med 1983; 308:862–867. **16.** Wynn V, Niththyananthan R. The effect of progestin in combined oral contraceptives on serum lipids with special reference to high-density lipoproteins. Am J Obstet Gynecol 1982; 142:766–771. **17.** Wynn V, Godsland I. Effects of oral contraceptives and carbohydrate metabolism. J Reprod Med 1986; 31 (9) (Supplement):892–897. **18.** LaRosa JC. Atherosclerotic risk factors in cardiovascular disease. J Reprod Med 1986; 31 (9) (Supplement):906–912. **19.** Inman WH, Vessey MP. Investigation of death from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 1968; 2 (5599):193–199. **20.** Maguire MG, Tonascia J, Sartwell PE, Stolley PD, Tockman MS. Increased risk of thrombosis due to oral contraceptives: a further report. Am J Epidemiol 1979; 110 (2):188–195. **21.** Pettiti DB, Wingerd J, Pellegrin F, Ramacharan S. Risk of vascular disease in women: smoking, oral contraceptives, noncontraceptive estrogens, and other factors. JAMA 1979; 242:1150–1154. **22.** Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. Br Med J 1968; 2 (5599):199–205. **23.** Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 1969; 2 (5658):651–657. **24.** Porter JB, Hunter JR, Danielson DA, Jick H, Stergachis A. Oral contraceptives and non-fatal vascular disease– recent experience. Obstet Gynecol 1982; 59 (3):299–302. **25.** Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception: an interim report. Biosocial Sci 1976; 8:375–427. **26.** Royal College of General Practitioners: Oral contraceptives, venous thrombosis, and varicose veins. J Royal Coll Gen Pract 1978; 28:393–399. **27.** Collaborative Group for the Study of Stroke in Young Women: Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med

1973; 288:871–878. **28.** Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. Lancet 1978; 2:234–236. **29.** Inman WH. Oral contraceptives and fatal subarachnoid hemorrhage. Br Med J 1979; 2 (6203):1468–70. **30.** Collaborative Group for the Study of Stroke in Young Women: Oral contraceptives and stroke in young women: associated risk factors. JAMA 1975; 231:718–722. **31.** Inman WH, Vessey MP, Westerholm B, Engelund A. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J 1970; 2:203–209. **32.** Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 35-mcg oestrogen preparations. Br Med J 1980; 280 (6224):1157–1161. **33.** Kay CR. Progestogens and arterial disease—evidence from the Royal College of General Practitioners' Study. Am J Obstet Gynecol 1982; 142:762–765. **34.** Royal College of General Practitioners: Incidence of arterial disease among oral contraceptive users. J Royal Coll Gen Pract 1983; 33:75–82. **35.** Ory HW. Mortality associated with fertility and fertility control: 1983. Family Planning Perspectives 1983; 15:50–56. **36.** The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of breast cancer. N Engl J Med 1986; 315:405–411. **37.** Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer risk in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 1983; 2:926–929. **38.** Paul C, Skegg DG, Spears GFS, Kaldor JM. Oral contraceptives and breast cancer: A national study. Br Med J 1986; 293:723–725. **39.** Miller DR, Rosenberg L, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer risk in relation to early oral contraceptive use. Obstet Gynecol 1986; 68:863–868. **40.** Olson H, Olson KL, Moller TR, Ranstam J, Holm P. Oral contraceptive use and breast cancer in young women in Sweden (letter). Lancet 1985; 2:748–749. **41.** McPherson K, Vessey M, Neil A, Doll R, Jones L, Roberts M. Early contraceptive use and breast cancer: Results of another case-control study. Br J Cancer 1987; 56:653–660. **42.** Huggins GR, Zucker PF. Oral contraceptives and neoplasia: 1987 update. Fertil Steril 1987; 47:733–761. **43.** McPherson K, Drife JO. The pill and breast cancer: why the uncertainty? Br Med J 1986; 293:709–710. **44.** Shapiro S. Oral contraceptives–time to take stock. N Engl J Med 1987; 315:450–451. **45.** Ory H, Naib Z, Conger SB, Hatcher RA, Tyler CW. Contraceptive choice and prevalence of cervical dysplasia and carcinoma in situ. Am J Obstet Gynecol 1976; 124:573–577. **46.** Vessey MP, Lawless M, McPherson K, Yeates D. Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. Lancet 1983; 2:930. **47.** Brinton LA, Huggins GR, Lehman HF, Malli K, Savitz DA, Trapido E, Rosenthal J, Hoover R. Long-term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 1986; 38:339–344. **48.** WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. Br Med J 1985; 209:961–965. **49.** Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan JR, Hill AP, Tyler CW. Epidemiology of hepatocellular adenoma: the role of oral contraceptive use. JAMA 1979; 242:644–648. **50.** Bein NN, Goldsmith HS. Recurrent massive hemorrhage from benign hepatic tumors secondary to oral contraceptives. Br J Surg 1977; 64:433–435. **51.** Klatskin G. Hepatic tumors: possible relationship to use of oral contraceptives. Gastroenterology 1977; 73:386–394. **52.** Henderson BE, Preston-Martin S, Edmondson HA, Peters RL,

Pike MC. Hepatocellular carcinoma and oral contraceptives. Br J Cancer 1983; 48:437–440. **53.** Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. Br Med J 1986; 292:1355–1357. **54.** Forman D, Vincent TJ, Doll R. Cancer of the liver and oral contraceptives. Br Med J 1986; 292:1357–1361. **55.** Harlap S, Eldor J. Births following oral contraceptive failures. Obstet Gynecol 1980; 55:447–452. **56.** Savolainen E, Saksela E, Saxen L. Teratogenic hazards of oral contraceptives analyzed in a national malformation register. Am J Obstet Gynecol 1981; 140:521–524. **57.** Janerich DT, Piper JM, Glebatis DM. Oral contraceptives and birth defects. Am J Epidemiol 1980; 112:73–79. **58.** Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R. Maternal hormone therapy and congenital heart disease. Teratology 1980; 21:225–239. **59.** Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979; 109:433–439. **60.** Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumors. Lancet 1973; 1:1399–1404. **61.** Royal College of General Practitioners: Oral contraceptives and health. New York, Pittman, 1974. **62.** Layde PM, Vessey MP, Yeates D. Risk of gallbladder disease: a cohort study of young women attending family planning clinics. J Epidemiol Community Health 1982; 36:274–278. **63.** Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO): Prevalence of gallstone disease in an Italian adult female population. Am J Epidemiol 1984; 119:796–805. **64.** Strom BL, Tamragouri RT, Morse ML, Lazar EL, West SL, Stolley PD, Jones JK. Oral contraceptives and other risk factors for gallbladder disease. Clin Pharmacol Ther 1986; 39:335–341. **65.** Wynn V, Adams PW, Godsland IF, Melrose J, Niththyananthan R, Oakley NW, Seedj A. Comparison of effects of different combined oral-contraceptive formulations on carbohydrate and lipid metabolism. Lancet 1979; 1:1045–1049. **66.** Wynn V. Effect of progesterone and progestins on carbohydrate metabolism. In Progesterone and Progestin. Edited by Bardin CW, Milgrom E, Mauvis- Jarvis P. New York, Raven Press, 1983 pp. 395–410. **67.** Perlman JA, Roussell-Briefel RG, Ezzati TM, Lieberknecht G. Oral glucose tolerance and the potency of oral contraceptive progestogens. J Chronic Dis 1985; 38:857–864. **68.** Royal College of General Practitioners' Oral Contraception Study: Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. Lancet 1977; 1:624. **69.** Fisch IR, Frank J. Oral contraceptives and blood pressure. JAMA 1977; 237:2499–2503. **70.** Laragh AJ. Oral contraceptive induced hypertension–nine years later. Am J Obstet Gynecol 1976; 126:141–147. **71.** Ramcharan S, Peritz E, Pellegrin FA, Williams WT. Incidence of hypertension in the Walnut Creek Contraceptive Drug Study cohort. In Pharmacology of Steroid Contraceptive Drugs. Garattini S, Berendes HW. Eds. New York, Raven Press, 1977 pp. 277–288. (Monographs of the Mario Negri Institute for Pharmacological Research, Milan). **72.** Stockley I. Interactions with oral contraceptives. J Pharm 1976; 216:140–143. **73.** The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of ovarian cancer. JAMA 1983; 249:1596–1599. **74.** The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. JAMA 1987; 257:796–800. **75.** Ory HW. Functional

ovarian cysts and oral contraceptives: negative association confirmed surgically. JAMA 1974; 228:68–69. **76.** Ory HW, Cole P, Macmahon B, Hoover R. Oral contraceptives and reduced risk of benign breast disease. N Engl J Med 1976; 294:419–422. **77.** Ory HW. The noncontraceptive health benefits from oral contraceptive use. Fam Plann Perspect 1982; 14:182–184. **78.** Ory HW, Forrest JD, Lincoln R. Making Choices: Evaluating the health risks and benefits of birth control methods. New York, The Alan Guttmacher Institute, 1983; p. 1. **79.** Schlesselman J, Stadel BV, Murray P, Lai S. Breast Cancer in relation to early use of oral contraceptives 1988; 259:1828–1833. **80.** Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, Stampfer MJ, Willett W, Peto R. A case-controlled study of oral contraceptive use and breast cancer. JNCI 1984; 72:39–42. **81.** LaVecchia C, Decarli A, Fasoli M, Franceschi S, Gentile A, Negri E, Parazzini F, Tognoni G. Oral contraceptives and cancers of the breast and of the female genital tract. Interim results from a case-control study. Br. J. Cancer 1986; 54:311–317. **82.** Meirik O, Lund E, Adami H, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use in breast cancer in young women. A Joint National Case-control study in Sweden and Norway. Lancet 1986; 11:650–654. **83.** Kay CR, Hannaford PC. Breast cancer and the pill–A further report from the Royal College of General Practitioners' oral contraception study. Br. J. Cancer 1988; 58:675–680. **84.** Stadel BV, Lai S, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. Contraception 1988; 38:287–299. **85.** Miller DR, Rosenberg L, Kaufman DW, Stolley P, Warshauer ME, Shapiro S. Breast cancer before age 45 and oral contraceptive use: New Findings. Am. J. Epidemiol 1989; 129:269–280. **86.** The UK National Case-Control Study Group, Oral contraceptive use and breast cancer risk in young women. Lancet 1989; 1:973–982. **87.** Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. Contraception 1989; 40:1–38. **88.** Vessey MP, McPherson K, Villard-Mackintosh L, Yeates D. Oral contraceptives and breast cancer: latest findings in a large cohort study. Br. J. Cancer 1989; 59:613–617. **89.** Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. Br. J. Cancer 1989; 59:618–621. **90.** Godsland, I et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990; 323:1375–81. **91.** Kloosterboer, HJ et al. Selectivity in progesterone and androgen receptor binding of progestogens used in oral contraception. Contraception, 1988; 38:325–32. **92.** Van der Vies, J and de Visser, J. Endocrinological studies with desogestrel. Arzneim. Forsch./Drug Res., 1983; 33(I),2:231–6. **93.** Data on file, Organon Inc. **94.** Fotherby, K. Oral contraceptives, lipids and cardiovascular diseases. Contraception, 1985; Vol. 31; 4:367–94. **95.** Lawrence, DM et al. Reduced sex hormone binding globulin and derived free testosterone levels in women with severe acne. Clinical Endocrinology, 1981; 15:87–91. **96.** Cullberg, G et al. Effects of a low-dose desogestrel-ethinyl estradiol combination on hirsutism, androgens and sex hormone binding globulin in women with a polycystic ovary syndrome. Acta Obstet Gynecol Scand, 1985; 64:195–202. **97.** Jung-Hoffmann, C and Kuhl, H. Divergent effects of two low-dose oral contraceptives on sex hormone-binding globulin and free testosterone. AJOG, 1987; 156:199–203. **98.** Hammond, G et al. Serum steroid binding protein concentrations, distribution of progestogens, and bioavailability of testosterone during treatment with contraceptives containing desogestrel or levonorgestrel. Fertil. Steril., 1984; 42:44–51. **99.** Palatsi, R et al. Serum total and

unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. Acta Derm Venereol, 1984; 64:517–23. **100.** Porter JB, Hunter J, Jick H et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985; 66:1–4. **101.** Porter JB, Jick H, Walker AM. Mortality among oral contraceptive users. Obstet Gynecol 1987; 7029-32. **102.** Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet, 1995; 346:1589–93. **103.** World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Lancet, 1995; 346:1582–88. **104.** Spitzer WO, Lewis MA, Heinemann LAJ, Thorogood M, MacRae KD on behalf of Transnational Research Group on Oral Contraceptives and Health of Young Women. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. Br Med J, 1996; 312:83–88.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Active tablets manufactured by: Organon (Ireland) Ltd., Swords, Co. Dublin, Ireland
Inert tablets manufactured by: N.V. Organon, Oss, The Netherlands

For patent information: www.merck.com/product/patent/home.html

The entities above are all subsidiaries of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA.

Revised: 06/2014

uspi-8276a-des-t-1406r003