Addressing Health Disparities at Community Level

BY JOEL B. FINKELSTEIN
Contributing Writer

WASHINGTON — Simple yet targeted efforts to improve minority patients' access to health care are growing in communities across the nation.

Often, language is the first component that needs to be addressed.

The first step in Expecting Success, a national project to reduce disparities supported by the Robert Wood Johnson Foundation, was to query patients on ethnicity and language on admission to 10 hospitals serving a large number of cardiac patients.

The results were somewhat startling: One hospital that had no interpreters, found that they were admitting 500 Spanish-speaking patients a month.

"Until you ask the question, you will not know. At that institution, they are now investing in interpreters, in translated materials, they started taking this seriously," said Dr. Bruce Siegel, director of Expecting Success and a professor of health policy at George Washington University.

In suburban Washington, Adventist Healthcare system was similarly surprised by the diversity of community it found that it serves.

"Within Washington Adventist Hospital, just one of our hospitals, we have 68 different languages spoken by our staff, serving a community with about 140 languages spoken," said Adventist Healthcare President William Robertson at a meeting that was sponsored by the Alliance of Minority Medical Associations, the National Association for Equal Opportunity in Higher Education, and the U.S. Health and Human Services department.

Even within an ethnic group, there is a wide diversity of cultures, said Maria Lemus, executive director of Vision y Compromiso, a California-based advocacy group that aims to educate the Hispanic community about quality of care issues.

"A Cuban is a very different Latino from a Mexican, from a Guatemalan. In terms of cultural competency and trying to adapt to your community, it is important to recognize those differences," Ms. Lemus commented.

Although understanding the ethnic make-up of a population is important before moving forward, successful strategies ultimately rely on the strengths of local communities, she noted.

The Promotoras Network involves community members who 'are always concerned about other people .... They are people with a heart to serve.'

One of the group's programs, the Community Health Worker/Promotoras Network, comprises respected members of the Hispanic community who provide education and outreach to their peers.

Ms. Lemus described *promotoras* as people who "are always concerned about other people … . They are people with a heart to serve."

The *promotoras* concept has been around for more 50 years, having been implemented in Europe, China, Africa, Europe, and Latin America. It was adopted in California a little more than 25 years ago, she said.

Promotora is an apt term for Jerry Barnes of Columbus, Ga., who gave up a successful nursing career to work toward a healthier community. As a city council member, he was the driving force behind an effort to reduce the city's relatively high diabetes rates.

"I had a 'eureka' moment one afternoon and thought, there are fire stations throughout the entire city. Why not make it accessible for people to stop in and have their blood sugar tested?" Mr. Barnes said.

Now thanks to the impetus of Mr. Barnes and the efforts of Columbus' mayor and fire chief, any resident can stop by one of the fire houses and have their blood sugar checked between 9:00 a.m and 9:00 p.m.

Officials in San Antonio took similar steps to ensure that widely needed services are readily available when they set up a twice-weekly immunization clinic at Goodwill Stores. The program was so successful that immunizations are now available 5 days a week.

Though home-grown, these strategies can be adapted to other communities as well, according to Ms. Lemus. ■

YAZ®
(drospirenone and ethinyl estradiol) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: YAZ® should not be used in women who have the following: •Renal insufficiency •Hepatic dysfunction •Adrenal Insufficiency • 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 • Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia • Undiagnosed abnormal genital bleeding • Cholestatic jaundice of pregnancy or jaundice with prior pill use • Known or suspected pregnancy • Liver tumor (benign or malignant) or active liver disease • Heavy smoking (≥15 cigarettes per day) and over age 35 • Hypersensitivity to any component of this product **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.

YAZ contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YAZ should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin – II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS. 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, stroke), hepatic neoplasia, gallbladder disease, and hypertension. The risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations 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 nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods. 1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS: a. Myocardial infarction: An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. b. 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 nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from 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, combined oral contraceptives should be started no earlier than four to six weeks after delivery and at that time only in women who elect not to breast feed. c. Cerebrovascular diseases: Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers 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. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired 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. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive. 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 preparations containing the lowest estrogen content that is judged appropriate for the individual patient. e. Persistence of risk of vascular disease: There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms 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. 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 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. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling. Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, 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 nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, women of all ages who take oral contraceptives, should take the lowest possible dose formulation that is effective. 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. Although the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combined oral contraceptives (RR=1.24), this excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use and no consistent 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 OC users tend to be less clinically advanced than in never users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive disease. 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. 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. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. 5. OCULAR LESIONS: There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives, which may lead to partial or complete loss of vision. 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. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when 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. (see **CONTRAINDICATIONS**) 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 dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed. 7. GALLBLADDER DISEASE: Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS: Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS** 1a. and 1d.), 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 (see **CONTRAINDICATIONS**). An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens. Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension 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 and there is no difference in the occurrence of hypertension among ever- and never-users. 10. HEADACHE: The onset or exacerbation of migraine or development of headache with a new pattern 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, 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. **PRECAUTIONS:** 1. General: **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: A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the 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. (See **WARNINGS** 1.d.) 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. Steroid hormones may be poorly metabolized in patients with impaired liver function. 5. FLUID RETENTION: Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and 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. 7. CONTACT LENSES: Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 8. DRUG INTERACTIONS: Effects of Other Drugs on Combined Hormonal Contraceptives: **Rifampin:** Metabolism of ethinyl estradiol and some progestins (e.g., norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin. **Minocycline:** Minocycline-related changes in estradiol, progesterone, FSH and LH plasma levels, breakthrough bleeding, or contraceptive failure cannot be ruled out. **Anticonvulsants:** Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness. **Antibiotics:** Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin—see above) on plasma concentrations of synthetic steroids. See also separate discussion on minocycline (above). **Atorvastatin:** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. **St. John's Wort:** 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 oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding. **Other:** Ascorbic acid and acetaminophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. **Effects of Drospirenone on Other Drugs:** Metabolic Interactions: Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see **Metabolism** section of the full package insert). In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*. Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. Interactions with Drugs that Have the Potential to Increase Serum Potassium: There is a potential for an increase in serum potassium in women taking YAZ with other drugs (see **BOLDED WARNING**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the clinical trials with YAZ. A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium Cmax and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.01 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L). Effects of Combined Hormonal Contraceptives on Other Drugs: Combined oral contraceptives containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives. 9. INTERACTIONS WITH LABORATORY TESTS: Certain endocrine- and liver-function tests and blood components may be affected by 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 and corticoids; however, free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives. 10. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See **WARNINGS**.) 11. PREGNANCY: Pregnancy category X. (See **CONTRAINDICATIONS** and **WARNINGS**) Estrogens and progestins should not be used during pregnancy. Fourteen pregnancies that occurred during exposure with 3 mg DRSP/0.03 mg EE tablets *in utero* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with the 3 mg DRSP/0.03 mg EE tablet is unknown. Twelve pregnancies that occurred with YAZ exposure *in utero* (none with more than a single cycle of exposure) have been identified. There were no known cases of congenital anomalies. A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day, 6 to 50 times the human exposure based on AUC of drospirenone, resulted in an increased number of fetuses with delayed ossification of bones of the feet in the two higher doses. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone, 2 to 27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol (100:1) during late pregnancy (the period of genital development) at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure. 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, 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. After oral administration of 3 mg DRSP/0.03 mg EE tablets about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant. 13. PEDIATRIC USAGE: Safety and efficacy of YAZ 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. **ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS**). • Thrombophlebitis • 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 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 or appetite (increase or decrease) • Change in cervical ectropion and secretion • Possible diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mood changes, including depression • Reduced tolerance to carbohydrates • Vaginitis, including candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • 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 a causal association has been neither confirmed nor refuted: • Acne • Budd-Chiari syndrome • Cataracts • Changes in libido • Colitis • Cystitis-like syndrome • Dizziness • Dysmenorrhea • Erythema multiforme • Erythema nodosum • Headache • Hemolytic uremic syndrome • Hemorrhagic eruption • Hirsutism • Impaired renal function • Loss of scalp hair • Nervousness • Optic neuritis, which may lead to partial or complete loss of vision • Pancreatitis • Premenstrual syndrome. The most frequent (> 1%) treatment-emergent adverse events, listed in descending order, reported with the use of YAZ in the contraception clinical trials, which may or not be drug related, included: upper respiratory infection, headache, breast pain, vaginal moniliasis, leukorrhea, diarrhea, nausea, vomiting, vaginitis, abdominal pain, flu syndrome, dysmenorrhea, moniliasis, allergic reaction, urinary tract infection, accidental injury, cystitis, tooth disorder, sore throat, infection, fever, surgery, sinusitis, back pain, emotional lability, migraine, suspicious Papanicolaou smear, dyspepsia, rhinitis, acne, gastroenteritis, bronchitis, pharyngitis, skin disorder, intermenstrual bleeding, decreased libido, weight gain, pain, depression, increased cough, dizziness, menstrual disorder, pain in extremity, pelvic pain, and asthenia. The most frequent (> 1%) treatment-emergent adverse events, listed in descending order, reported with the use of YAZ in the PMDD clinical trials, which may or not be drug related, included: intermenstrual bleeding, headache, nausea, breast pain, upper respiratory infection, asthenia, abdominal pain, decreased libido, emotional lability, suspicious Papanicolaou smear, nervousness, menorrhagia, pain in extremity, depression, menstrual disorder, migraine, sinusitis, weight gain, vaginal moniliasis, vaginitis, hyperlipidemia, back pain, diarrhea, increased appetite, enlarged abdomen, accidental injury, acne, dysmenorrhea, and urinary tract infection. The most frequent (> 1%) treatment-emergent adverse events, listed in descending order, reported with the use of YAZ in the acne clinical trials, which may or not be drug related, included: upper respiratory infection, metrorrhagia, headache, suspicious Papanicolaou smear, nausea, sinusitis, vaginal moniliasis, flu syndrome, menorrhagia, depression, emotional lability, abdominal pain, gastroenteritis, urinary tract infection, tooth disorder, infection, vomiting, pharyngitis, breast pain, dysmenorrhea, menstrual disorder, accidental injury, asthenia, sore throat, weight gain, arthralgia, bronchitis, rhinitis, amenorrhea, and urine abnormality. **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of other oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. Drospirenone, however, is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Manufactured for:
Bayer HealthCare
Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Germany

© 2007, Bayer HealthCare Pharmaceuticals Inc. All rights reserved. Printed in USA 6061602BH March 2007