

# Movement seeks consensus on Health Reform

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The way Dr. John A. Kitzhaber sees it, Americans can't afford to sit back and wait for the future of health care to unfold before them; they should assume an active role in shaping its future.

"If people are unable or unwilling to agree among themselves on a vision for the future, the political process cannot and will not do it for them—and we will be

destined to continue to be shackled to the failed policies of the past," he warned at the November 2007 annual meeting of the Society of Clinical Surgery in Portland, Ore. "By default, we will be allowing our future to become a matter of chance rather than a matter of choice. I think we are better than that."

In January 2006, Dr. Kitzhaber, the former governor of Oregon, founded the Archimedes Movement, a grassroots organization that takes a "we can do better" ap-

proach to the governance and delivery of health care. The movement is "committed to providing a safe forum in which citizens and stakeholders alike can be brought together to create a shared vision of a new health care system, a space in which we can ask, 'If anything were possible, what would a better system look like?'" he said.

The name refers to Archimedes, the mathematician who invented the lever and a place to stand, and I can move the Earth."

A key strategy of the effort is to agree on what a new health care system should look like, and to expose the contradictions and inequities of the current system and create a "tension" between the status quo and a vision for a new system.

Dr. Kitzhaber, an emergency physician who governed Oregon from 1995 to 2003, said he believes there should be a different standard for the part of health care that is financed by public resources and the portion that is financed by private resources. "We must demand that we get an actual health benefit for the public dollars we allocate for health care, a positive return on investment, [and] the effective and efficient use of public tax dollars. And, since these



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DR. KITZHABER

are public resources—resources held in common—we must demand that their allocation benefits all of our citizens, not just some of them; that it does not leave 47 million people behind."

As an example, he said that people who wish to buy an expensive brand name drug when a much cheaper generic is just as effective clinically, and just as safe, should be able to do so with their own personal resources. Public resources should not be used to subsidize the difference in cost. Similarly, he said that expectant parents who want an ultrasound to determine the sex of their unborn child when the procedure is not indicated clinically for a normal term pregnancy should be able to get that—but again, the cost should not be subsidized with public resources.

To date, the Archimedes Movement has conducted public forums and vision-sharing meetings with more than 3,000 Oregonians in 30 chapters, 13 hospital CEOs, 11 insurer and health plan executives, dozens of physicians and nurses, leaders of national state and labor organizations, and representatives of more than 50 non-health-related businesses in the state.

The resulting consensus led to the Oregon Better Health Act, which was introduced in the 2007 Oregon legislature as Senate Bill 27. It proposes that Oregonians have access to a "core benefit" of essential health services, and seeks to realign financial incentives to ensure fair and reasonable payment to providers, value-based cost sharing for consumers, and a transition to a more efficient delivery system.

Although SB 27 did not pass in the 2007 session, the enthusiasm it generated from citizens and stakeholders propelled the Archimedes Movement into the limelight. It also produced three documents that offer a conceptual framework for a new system in the state and that may serve as a foundation for bringing about national reform. The documents—a Statement of Intent, Principles, and a Framework—are available at [www.wecandobetter.org](http://www.wecandobetter.org).

## 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 thrombotic complications •Severe hypertension •Diabetes mellitus 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 supplements, 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 estrogen 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. Through careful 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: 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 times. 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 these women, oral contraceptives 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. 2. 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 1 for new cases of about 4.5 for new cases requiring hospitalization. The risk of thromboembolism and other vascular diseases (thrombotic and hemorrhagic strokes), 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. 3. 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 1 for new cases of about 4.5 for new cases requiring hospitalization. The risk of thromboembolism and other vascular diseases (thrombotic and hemorrhagic strokes), 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. 4. 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 the 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 described should be the 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 childbearing. 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 is not statistically significant after 10 years after discontinuation. 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 tumor. Some studies suggest that oral contraceptive use has not 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 LATE IN 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 the first trimester of pregnancy, although some concerns are expressed, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce abortion 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 in oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptives with lower hormonal doses of estrogen and progestogen. 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, pre-diabetic and diabetic women should be carefully observed while taking oral contraceptives. A small proportion of women will have significant hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a, and 1b), 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. This may be considered a normal side effect of the treatment and measures taken to minimize the occurrence of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or 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 may 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 Oral 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. **Miconazole:** Miconazole-related changes in estradiol, progesterone, FSH and LH plasma levels, breakthrough bleeding, or contraceptive failure cannot be ruled out. **Anticoagulants:** Anticoagulants 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 miconazole (above). **Atorvastatin:** Co-administration 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 Drospirenone:** Drospirenone is metabolized to drospirenone P450 (DPP) by 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 CYP2A2 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 **BOLD WARNING**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the clinical trials with YAZ. A causal association with renal impairment and acute renal failure was not observed in any of the clinical trials. **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 harden 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 + 0.03, 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 vitro* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with serious congenital malformations was not observed. Twelve pregnancies that occurred with YAZ exposure *in vitro* (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 cynomolgus 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 0.3 mg of 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**): • 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 • 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 • Pseudotumor • Premenstrual syndrome. The most frequent (> 1%) treatment-emergent adverse events, listed in descending order, reported with the use of YAZ in the contraceptive 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 Papaniolou 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 asthma. 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, asthma, abdominal pain, decreased libido, emotional lability, suspicious Papaniolou smear, nervousness, menorrhagia, pain in extremity, depression, menstrual disorder, migraine, sinusitis, weight gain, nervousness, vaginitis, hyperhidrosis, breast pain, diarrhea, increased cough, dizziness, increased abdominal, 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 Papaniolou 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, asthma, 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 derivative and has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Manufactured for:  
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