

New Data Reinforce Valproate-Birth Defects Link

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BOSTON — Two new data sets reinforce the recommendation to avoid valproate as a first-line therapy for any indication in women of childbearing years.

The findings, presented at the annual meeting of the American Academy of Neurology, strengthen evidence of a link between valproate use and an increased risk of major congenital malformations as

well as impaired cognitive development of children exposed in utero.

“Not only our study, but nine other studies on valproate’s anatomical and behavioral effects, have shown similar signals of poor outcome with this drug,” Dr. Kimford J Meador commented. “The drug should not be a first-line therapy for any indication in women of childbearing age. At the very minimum, women need to be aware of these risks if they are going to take this drug. We need to remember that

half of U.S. pregnancies are unplanned.”

Dr. Meador, the Melvin Greer Professor of Neurology and director of the epilepsy program at the University of Florida, Gainesville, presented interim data from the ongoing Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study for which investigators enrolled 185 children whose mothers took carbamazepine (48), lamotrigine (66), phenytoin (42), or valproate (29) for epilepsy during pregnancy. Data were given on the children’s mental

development at 2 years; the prospective study will follow the cohort to age 6.

Mean IQ scores based on the Mental Development Index (MDI) from the Bayley Scale were lowest for children in the valproate group (81), Dr. Meador said. A score below 85 is considered to be below normal limits. Mean scores in the other groups were 94 for lamotrigine, 95 for phenytoin, and 96 for carbamazepine.

In addition, he said, the percentage of children in the valproate group with an MDI of less than 70 (correlating with mental retardation) was 24%, about double that seen in any of the other groups (carbamazepine, 13%; lamotrigine, 11%; and phenytoin, 12%).

The study also found an inverse relationship between maternal valproate blood levels during pregnancy and MDI scores in the children, Dr. Meador noted. All of the valproate relationships remained constant even after maternal IQ—an important driver of childhood IQ, maternal epilepsy type, and past medical history were controlled for.

The mechanism of brain injury in the valproate group is probably third-trimester neuronal apoptosis, Dr. Meador said in an interview. “We think it’s similar to what’s seen in fetal alcohol syndrome, and the apoptosis appears to occur at a relatively lower dose than it would with other drugs, such as phenytoin. I think that’s why we see such an increased signal.”

NEAD only includes the children of women with epilepsy—the group that accounts for the smallest proportion of valproate scrips, he added. “Most of the prescriptions are written for other things, including psychotropic and pain indications. [Fewer] than half are for epilepsy.”

In the third quarter of 2006, about 16% of women of childbearing age with epilepsy were taking the drug, making it the fourth leading antiepileptic in the United States for this group. Valproate sales jumped 28% last year, an increase “that has to include some portion of women of childbearing age,” Dr. Meador said.

The second study, GlaxoSmithKline’s lamotrigine pregnancy registry, found that valproate in conjunction with lamotrigine significantly increases the risk of a major birth defect. Lamotrigine is a GSK product.

The registry, now in its 14th year, has prospectively enrolled 2,400 pregnancies occurring in 32 countries. There are known outcome data on 1,539 pregnancies, said Marianne Cunningham, Ph.D., of GSK.

The risk of a major birth defect in the 908 first-trimester exposures to lamotrigine only was 2.9%, similar to the background population risk of 2%-3%. The risk associated with nonvalproate polytherapy was 2.6%. However, when lamotrigine polytherapy included valproate, the risk of a major congenital malformation jumped to more than 11%.

“We have a signal for an increased risk for polytherapy including valproate,” she said, although “it’s unclear whether valproate is responsible for this increased risk.”

Dr. Meador noted, however, that six other studies have concluded that valproate significantly increases the risk of birth defects. ■

NUVARING® (etonogestrel/ethinyl estradiol vaginal ring)

Rx only. For vaginal use only.

Brief Summary of Full Prescribing Information

Women should be cautioned that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases. INDICATIONS AND USAGE: NuvaRing® is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. Like oral contraceptives, NuvaRing® is highly effective if used as recommended in this label. In three large clinical trials of 13 cycles of NuvaRing® use, pregnancy rates were between one and two per 100 women-years of use. Table III lists the pregnancy rates for users of various contraceptive methods.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from combination 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 combination hormonal contraceptives, including NuvaRing®, should be strongly advised not to smoke.

NuvaRing® and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. There is no epidemiologic data available to determine whether safety and efficacy with the vaginal route of administration of combination hormonal contraceptives would be different than the oral route. The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. The information contained in this package insert is principally based on studies carried out in women 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 oral contraceptives with 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. 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 three for the first episode of superficial venous thrombosis, four to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to six for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about three for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolism associated with oral contraceptives is not related to length of use and disappears after pill use is stopped. Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel), the progestin in NuvaRing®, is the biologically active metabolite of desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional one to two 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. It is unknown if NuvaRing® has a different risk of venous thromboembolism than second generation oral contraceptives. A two- to four-fold increase in 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, combination hormonal contraceptives, including NuvaRing®, should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, combination hormonal contraceptives, such as NuvaRing®, should be started no earlier than four to six weeks after delivery in women who elect not to breast-feed. The clinician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, NuvaRing® should be discontinued immediately. **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 combination oral contraceptive users has been estimated to be two to six. 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. 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 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 WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. NuvaRing® must be used with caution in women with cardiovascular disease. **Cerebrovascular disease.** Cerebrovascular disease, including 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 for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from three for non-smokers to users to 14 for users with severe hypertension. 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, 1.3 for non-smokers who used oral contraceptives, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. 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 progestogens used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive. **4. PERSISTENT RISK OF VASCULAR DISEASE.** There are two studies that 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 nine 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. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least six 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 more of ethinyl estradiol. **5. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE.** One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (Table V in the full prescribing information). 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 age 35 and older who smoke and age 40 and older who do not smoke, mortality associated with birth control is low compared with that associated with childbirth. The overall mortality rate shows a slight increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s, but not reported until 1983. However, current clinical practice involves the use of lower estrogen-dose formulations combined with careful consideration of risk factors. 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 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. Although the data are mainly obtained with oral contraceptives, this is likely to apply to NuvaRing® as well. Women of all ages who take hormonal contraceptives, should take the lowest possible dose formulation that is effective and meets the needs of the individual woman. **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 combination oral contraceptives. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users. Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormonally sensitive tumor. Some studies suggest that combination 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. It is unknown whether NuvaRing® is distinct from oral contraceptives with regard to the above statements. **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 per 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 US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. It is unknown whether NuvaRing® is distinct from oral contraceptives in this regard. **5. Ocular Lesions.** There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. NuvaRing® 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. HORMONAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY.** Hormonal contraceptives should not be used during pregnancy. Extensive epidemiologic 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 oral contraceptives are taken inadvertently during early pregnancy. Combination hormonal contraceptives, such as NuvaRing®, should not be used to induce withdrawal bleeding as a test for pregnancy. NuvaRing® should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any woman who has not adhered to the prescribed regimen for use of NuvaRing® and has missed a menstrual period or who has missed two consecutive periods, pregnancy should be ruled out. **7. GALLBLADDER DISEASE.** Combination hormonal contraceptives, such as NuvaRing®, may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combination hormonal contraceptive use. **8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS.** Hormonal contraceptives have been shown to cause a decrease in glucose tolerance in some users. However, in the non-diabetic woman, combination hormonal contraceptives appear to have no effect on fasting blood glucose. Prediabetic and diabetic women should be carefully observed while taking combination hormonal contraceptives, such as NuvaRing®. In a clinical study involving 37 NuvaRing®-treated subjects, glucose tolerance

tests showed no clinically significant changes in serum glucose levels from baseline to cycle six. A small proportion of women will have persistent hypertriglyceridemia while using oral contraceptives. Changes in serum triglycerides and lipoprotein levels have been reported in combination hormonal contraceptive users. **9. ELEVATED BLOOD PRESSURE.** An increase in blood pressure has been reported in women taking oral contraceptives and the increase is 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 these women elect to use NuvaRing®, they should be monitored closely and if significant elevation of blood pressure occurs, NuvaRing® should be discontinued. For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former 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 NuvaRing® and evaluation of the cause. **11. BLEEDING IRREGULARITIES, Bleeding Patterns.** Breakthrough bleeding and spotting are sometimes encountered in women using NuvaRing®. If abnormal bleeding while using NuvaRing® persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology or pregnancy, and appropriate treatment should be instituted when necessary. In the event of amenorrhea, pregnancy should be ruled out. Bleeding patterns were evaluated in three large clinical studies. In the US-Canadian study (n=1177), the percentages of subjects with breakthrough bleeding/spotting ranged from 7.2 to 17.7% during cycles 1-13. In the two non-US studies, the percentages of subjects with breakthrough bleeding/spotting ranged from 2.6 to 8.4% (Study 1, n=145 European and Israeli subjects) and from 2.0 to 8.7% (Study 2, n=512 European and South American subjects). In these three studies, the percentages of women who did not have withdrawal bleeding in a given cycle ranged from 0.3 to 3.8%. Some women may encounter amenorrhea or oligomenorrhea after discontinuing use of NuvaRing®, especially when such a condition was pre-existent. **12. ECTOPIC PREGNANCY.** Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. **PRECAUTIONS. 1. GENERAL. Women should be cautioned that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases. 2. PHYSICAL EXAMINATION AND FOLLOW-UP.** It is routine medical practice for women using NuvaRing®, as for all women, to have an annual medical evaluation including physical examination and relevant laboratory tests. The physical examination should include special reference to blood pressure, breasts, abdomen, pelvic organs and vagina (including cervical cytology). In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a 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 NuvaRing®. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. **LIVER FUNCTION.** If jaundice develops in any woman using NuvaRing®, the product should be discontinued. The hormones in NuvaRing® may be poorly metabolized in women with impaired liver function. **5. FLUID RETENTION.** Steroid hormones like those in NuvaRing®, may cause some degree of fluid retention. NuvaRing® should be prescribed with caution, and only with careful monitoring, in women with conditions which might be aggravated by fluid retention. **6. EMOTIONAL DISORDERS.** Women who become significantly depressed while using combination hormonal contraceptives, such as NuvaRing®, should stop the medication and use another 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 NuvaRing® discontinued if significant depression occurs. **7. TAMPOON USE.** On rare occasions, NuvaRing® may be expelled while removing a tampon (see EXPULSION). Users should be advised that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing®. **8. TOXIC SHOCK SYNDROME (TSS).** Cases of toxic shock syndrome have been associated with tampons and certain barrier contraceptives. Very rare cases of TSS have been reported by NuvaRing® users; in some cases the women were also using tampons. No causal relationship between the use of NuvaRing® and TSS has been established. If a patient exhibits signs or symptoms of TSS, the possibility of this diagnosis should not be excluded and appropriate medical evaluation and treatment initiated. **9. CONTACT LENSES.** Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by their optometrist. **10. DRUG INTERACTIONS.** Changes in Contraceptive Effectiveness Associated with Co-administration of Other Drugs. Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and modafinil. Women may need to use an additional contraceptive method when taking such medications. Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes in the efficacy of the oral contraceptives and the effectiveness of the anti-HIV protease inhibitors have been observed. The effectiveness and safety of oral contraceptive products may be affected; it is unknown whether this applies to NuvaRing®. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information. 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 oral contraceptives containing ethinyl estradiol increase AUC valproic acid and plasma concentrations of acyclovir. Acetylsalicylic acid and acetaminophen may increase plasma levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels. Co-administration of vaginal minocycline nitrate and NuvaRing® increases the serum concentrations of etonogestrel and ethinyl estradiol by up to 40%. **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. In addition, oral contraceptives may induce the conjugation of other compounds. Increased plasma concentrations of acetaminophen and increased clearance of diazepam, clonazepam, and chlorzoxazone have been reported. Other drugs which have been studied with oral contraceptives include: **11. INTERACTIONS WITH LABORATORY TESTS.** Certain endocrine and liver function tests and blood components may be affected by combined hormonal contraceptives: a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin III, 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 globulin is increased and results 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 NuvaRing®. **12. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY.** In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 µg etonogestrel per day (approximately 0.3 and 0.6 times the systemic steady-state exposure of women using NuvaRing®), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility returned after withdrawal from treatment (see WARNINGS). **13. PREGNANCY. Pregnancy Category X (see CONTRAINDICATIONS in the full prescribing information and WARNINGS).** Teratology studies have been performed in rats and rabbits using the oral route of administration at doses up to 130 and 260 times, respectively, the human NuvaRing® dose (based on body surface area) and have revealed no evidence of harm to the fetus due to etonogestrel. **14. NURSING MOTHERS.** The effects of NuvaRing® in nursing mothers have not been evaluated and are unknown. Small amounts of 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, contraceptive steroids given in the postpartum may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of children whose mothers used combination hormonal contraceptives while breast-feeding has shown no deleterious effects on infants. However, women who are breast-feeding should be advised not to use NuvaRing® but to use other forms of contraception until the child is weaned. **15. PEDIATRIC USE.** Safety and efficacy of NuvaRing® have 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. **16. GERIATRIC USE.** There are no clinical studies in geriatric patients. **17. MAJOR ADVERSE REACTIONS.** NuvaRing® may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Some women are aware of the ring at random times during the 21 days of use or during intercourse. During intercourse some sexual partners may feel NuvaRing® in the vagina. However, clinical studies revealed that 90% of couples did not find this to be a problem. NuvaRing® may interfere with the correct placement and position of a diaphragm. A diaphragm is therefore not recommended as a back-up method with NuvaRing® use. **18. EXPULSION.** NuvaRing® can be accidentally expelled, for example, while removing a tampon, during intercourse, or with straining during a bowel movement. NuvaRing® should be left in the vagina for a continuous period of three weeks. If the ring is accidentally expelled and is left outside of the vagina for less than three hours contraceptive efficacy is not reduced. NuvaRing® can be rinsed with cool to lukewarm (not hot) water and reinserted as soon as possible, but at the latest within three hours. If NuvaRing® is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration. **If NuvaRing® is out of the vagina for more than three continuous hours: During Weeks 1 and 2:** If NuvaRing® has been out of the vagina for more than three continuous hours during the 1st or 2nd week of use, contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. **During Week 3:** If NuvaRing® has been out of the vagina for more than three continuous hours during the 3rd week of the three-week use period, the woman should discard that ring. One of the following two options should be chosen: 1. Insert a new ring immediately. Inserting a new ring will start the next three-week use period. The woman may not experience a withdrawal bleed from her previous cycle. However, breakthrough spotting or bleeding may occur. 2. Have a withdrawal bleed and insert a new ring no later than seven days (7x24 hours) from the time the previous ring was removed or expelled. This option should only be chosen if the ring was used continuously for the preceding seven days. A barrier method such as condoms or spermicides must be used until the new ring has been used continuously for seven days. **During Week 3:** If NuvaRing® has been out of the vagina for more than three continuous hours during the 3rd week of the three-week use period, the woman should discard that ring. One of the following two options should be chosen: 1. Insert a new ring immediately. Inserting a new ring will start the next three-week use period. The woman may not experience a withdrawal bleed from her previous cycle. However, breakthrough spotting or bleeding may occur. 2. Have a withdrawal bleed and insert a new ring no later than seven days (7x24 hours) from the time the previous ring was removed or expelled. This option should only be chosen if the ring was used continuously for the preceding seven days. A barrier method such as condoms or spermicides must be used until the new ring has been used continuously for seven days. **19. DISCONNECTED RING.** There have been reported cases of NuvaRing® disconnecting at the weld joint. This is not expected to affect the contraceptive effectiveness of NuvaRing®. In the event of a disconnected ring, vaginal discomfort or expulsion (slipping out) is more likely to occur (see EXPULSION). If a woman discovers that her NuvaRing® has disconnected, she should discard the ring and replace it with a new ring. **ADVERSE REACTIONS.** The most common adverse events reported by five to 14% of women using NuvaRing® in clinical trials (n=2501) were the following: vaginitis, headache, upper respiratory tract infection, vaginal secretion, sinusitis, weight gain, and nausea. The most frequent system-organ class adverse events leading to discontinuation in one to 2.5% of women using NuvaRing® in the trials included the following: device-related events (foreign body sensation, colitis, proctitis, device expulsion), vaginal symptoms (discomfort/vaginitis/vaginal secretion), headache, emotional lability, and weight gain. Listed below are adverse reactions that have been associated with the use of combination hormonal contraceptives. These are also likely to apply to combination vaginal hormonal contraceptives, such as NuvaRing®. An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (see CONTRAINDICATIONS in the full prescribing information and WARNINGS): Thrombophlebitis and venous thrombosis with or without embolism; Arterial thromboembolism; Pulmonary embolism; Myocardial infarction; Overtaking of lactation when given immediately postpartum; Hypertension; Gallbladder disease; Hepatic adenomas or benign liver tumors. There is evidence of an association between the following conditions and the use of combination hormonal contraceptives: Mesenteric thrombosis; Retinal thrombosis. The following additional adverse reactions have been reported in users of combination hormonal 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 (increase or decrease); Change in cervical erosion and secretion; Diminution in lactation when given immediately postpartum; Cholestatic jaundice; Migraine; Rash (allergic); Mental depression; Reduced tolerance to carbohydrates; Vaginal candidiasis; Change in corneal curvature (steepening); Intolerance to contact lenses. The following additional adverse reactions have been reported in users of combination hormonal contraceptives and a causal association has been further confirmed or refuted: Pre-menstrual syndrome; Catarracts; Changes in appetite; Cystitis-like syndrome; Headache; Nervousness; Dizziness; Hirsutism; Loss of scalp hair; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Vaginitis; Porphyria; Impaired renal function; Hemolytic uremic syndrome; Acne; Changes in libido; Colitis; Budd-Chiari Syndrome. **OVERDOSE.** Overdose of combination hormonal contraceptives may cause nausea, vomiting, vaginal bleeding, or other menstrual irregularities. Given the nature and dose of NuvaRing®, it is unlikely that overdose will occur. If NuvaRing® is broken, it does not release a higher dose of hormones. Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. There are no antidotes and further treatment should be symptomatic.

For additional product information, please call 1-866-4NUVARING or visit www.NuvaRing.com <http://www.nuvaring.com/>. Manufactured for Organon USA, Inc., Roseland, NJ 07068, by N.V. Organon, Oss, The Netherlands © 2005 Organon USA Inc. 75137 NUV-8012 8/05 20