Merck Stands Behind the Safety Profile of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

Terms: Company Statements

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Nothing is more important to Merck than the safety of our medicines and vaccines and the people who use them. Merck employees, and our families, use Merck medicines, too. Our deepest sympathies go out to those who are suffering from an injury or loss of a loved one.

There is substantial evidence to support the safety profile and efficacy of NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), which delivers 0.120 mg etonogestrel/0.015 mg ethinyl estradiol per day. We encourage women to work jointly with their healthcare providers to discuss the benefits and risks of any contraceptive method before choosing an option that is right for them. Among other considerations, women should understand important information about venous thromboembolic events (VTE), such as deep vein thrombosis and pulmonary embolism, when making their choice of contraception.

All combined hormonal contraceptives (CHCs), including NuvaRing and combined oral contraceptives (COCs), are associated with an increased risk of VTEs. Two recent studies – a prospective, large cohort study sponsored by the company and a retrospective observational study sponsored by the U.S. Food and Drug Administration (FDA) – found that the risk of blood clots for new users of NuvaRing is similar to the risk for new users of COCs.

All CHCs in the U.S., including NuvaRing, have a Boxed Warning on the increased risk of serious cardiovascular events, especially in women who smoke. Both the FDA-approved patient information and the physician package labeling for NuvaRing have included this information since the product was approved in 2001, and both were updated in October 2013 to include the information noted above showing that the risk of blood clots for new users of NuvaRing is similar to the risk for new users of COCs.

In general, the absolute VTE rates are increased for women who use CHCs compared to those who do not use CHCs. However, the rates of VTEs associated with pregnancy are even greater than those for women who use CHCs, especially during the post-partum period. To put this risk in perspective, as described both the Patient and the Prescribing Information for NuvaRing, it is estimated that:

- If 10,000 women who are not pregnant and do not use CHCs are followed for one year, 1 to 5 of these women, will develop a VTE;
- If 10,000 women who use a CHC are followed for one year, 3 to 12 women will develop a VTE;
- If 10,000 women who are pregnant (and not taking a CHC) are followed for one year, 5 to 20 women will develop a VTE;
- If 10,000 women who are postpartum (12 weeks after delivery) are followed for one year, 40 to 65 will develop a VTE.

We stand behind the research that supported the approval of NuvaRing, and our continued work to monitor the safety of the medicine. Merck is pleased to be able to offer an alternative to the pill for women seeking to avoid unintended pregnancy and for whom a CHC is deemed medically appropriate by their healthcare providers.

Additional Background on the Safety Profile of NuvaRing (etonogestrel/ethinyl estradiol vaginal ring)

Organon, with academic and other researchers, conducted and published well-controlled clinical trials involving more than 3,700 women that demonstrated the medicine's efficacy and safety. The results of these trials were provided to regulatory agencies, and the medicine was approved by the FDA in 2001.

The risk of thrombotic events (which includes VTE) associated with the use of NuvaRing was studied in a large observational trial of 33,295 women, a study funded by Merck. The study investigated the risk of VTE for new users, and women who were switching to or restarting NuvaRing or COCs in a population representative of routine clinical users. In this study, more than 16,800 women used NuvaRing. The study, Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC), was recently published in Obstetrics & Gynecology in 2013 and was presented at American Congress of Obstetricians and Gynecologists in 2012. The results of TASC indicated that use of NuvaRing and COCs were associated with similar VTE risk.

A separate, FDA-funded study in Kaiser Permanente and Medicaid databases, which was a retrospective cohort study using data from four health plans in the U.S., also examined the risk of thrombotic events in new users of NuvaRing. In that study, the risk of VTE for new users of NuvaRing, relative to new users of COCs[11], was not increased.

Following completion of the TASC study, Merck worked closely with regulatory agencies to update labels for NuvaRing worldwide to include these results. The label for NuvaRing was updated in 2013 in the U.S., Canada, and Europe to reflect these results.
[1] Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel.

Resolution of Litigation

As previously disclosed, Merck has reached an agreement to resolve the NuvaRing product liability claims in the U.S. as of February 7, 2014, including cases filed in the federal multidistrict litigation; in the New Jersey state coordinated proceedings; and in other state and federal proceedings. An immaterial number of cases have opted out of the settlement. Merck does not admit wrongdoing under the agreement, and the company will pay $100 million to resolve the claims filed in federal or state court, as well as certain unfiled claims. The company has insurance coverage available to it that will be used to fund the settlement. On June 4, 2014, it was confirmed that the resolution will move forward as planned.

About NuvaRing (etonogestrel/ethinyl estradiol vaginal ring)

NuvaRing is a flexible birth control vaginal ring used to prevent pregnancy. Since June 2002, more than 44 million prescriptions for NuvaRing have been filled in the U.S., and NuvaRing is currently available in more than 50 countries around the world.

Selected Safety Information

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. The risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NuvaRing, should not be used by women who are over 35 years of age and smoke.

Patients Who Should Not Use NuvaRing

NuvaRing is contraindicated in women who are known to have a high risk of arterial or venous thrombotic diseases, women who have liver tumors or liver disease, undiagnosed abnormal uterine bleeding, breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past, or if they are pregnant.

Serious Risks With NuvaRing

- **Thromboembolic and Other Vascular Events**: The use of a CHC, like NuvaRing, is associated with increased risks of several serious side effects, including blood clots, stroke, or heart attack, especially in women with other risk factors for these events. Some studies suggest that the risk is increased by combination oral contraceptives containing desogestrel (etonogestrel is the biologically active metabolite of desogestrel); other studies do not support this finding. Stop NuvaRing if an arterial thrombotic or venous thromboembolic event (VTE) occurs. The risk of VTE is highest during the first year of CHC use and after restarting a CHC following a break of at least 4 weeks. Stop NuvaRing at least 4 weeks before and for 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism, and during and following prolonged immobilization. Start NuvaRing no earlier than 4 weeks after delivery, in women who are not breastfeeding.

- **Toxic Shock Syndrome (TSS)**: If signs and symptoms of TSS are present, initiate appropriate medical evaluation and treatment.

- **Liver Disease**: Disturbances of liver function may require CHC discontinuation until liver function markers return to normal and CHC causation has been excluded. Discontinue NuvaRing if jaundice develops.

- **High Blood Pressure**: For women with well-controlled hypertension, monitor blood pressure and stop NuvaRing if blood pressure rises significantly. An increase in blood pressure is more likely in older women and with extended duration of use.

- **Carbohydrate and Lipid Metabolic Effects**: Monitor prediabetic and diabetic women using NuvaRing and consider alternative contraception for women with uncontrolled dyslipidemia.

- **Headache**: Consider discontinuation of NuvaRing in women who develop new onset of headaches that are recurrent, persistent, or severe, or in the case of increased frequency or severity of migraine.

- **Bleeding Irregularities**: Evaluate irregular bleeding or amenorrhea for causes such as pregnancy or malignancy.

Most Common Adverse Reactions

- The most common adverse reactions reported by ≥2% of women (n=2,501) using NuvaRing in clinical trials were: vaginitis (13.8%), headache (including migraine) (11.2%), mood changes (eg, depression, mood swings, mood altered, depressed mood, affect lability) (6.4%), device-related events (eg, expulsion/discomfort/foreign-body sensation) (6.3%), nausea/vomiting (5.9%), vaginal discharge (5.7%), increased weight (4.9%), vaginal discomfort (4.0%), breast pain/discomfort/tenderness (3.8%), dysmenorrhea (3.5%), abdominal pain (3.2%), acne (2.4%), and decreased libido (2.0%).

Counsel patients that NuvaRing does not protect against HIV infection (AIDS) and other sexually transmitted infections.
About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit [www.merck.com](http://www.merck.com).

Forward-Looking Statement

This statement includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck’s management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck’s 2013 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).


**NuvaRing® is a registered trademark of Merck Sharp & Dohme B.V., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.**

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