## VI.2 Elements for a Public Summary

### VI.2.1 Overview of Disease Epidemiology

Etonogestrel/ethinylestradiol vaginal delivery system is a vaginal ring form of birth control used to prevent unplanned pregnancy in healthy women of childbearing potential. Many options are available for hormonal birth control, including oral tablets, and implants under the skin: the etonogestrel/ethinylestradiol vaginal delivery system is the only available hormonal birth control that is administered through the vagina. An unplanned pregnancy is a pregnancy that is either mistimed or unwanted at the time of conception. Of the approximately 208 million pregnancies that occurred worldwide in 2008, it is estimated that 41% or 85 million were unplanned. Rates of unplanned pregnancies in North America and Europe were 47% and 44%, respectively.

Prenatal and perinatal consequences of unplanned pregnancy include delays in seeking prenatal care and increased risk of low weight babies, as well as longer-term consequences for the infant and mother including poor physical and mental health.

### VI.2.2 Summary of Treatment Benefits

The main studies of etonogestrel/ethinylestradiol vaginal delivery system included 3,592 adult women who were in need of birth control. Women in these studies were randomly assigned to etonogestrel/ethinylestradiol vaginal delivery system or to one of the following combined oral birth control methods for at least one year of use (13 or more cycles): levonorgestrel/ethinylestradiol pills or drospirenone/ethinylestradiol pills. In these studies, the chance of getting pregnant with etonogestrel/ethinylestradiol vaginal delivery system was about 1 to 2% a year. This means that, for every 100 women who used this ring for one year, one or two became pregnant. The chance of getting pregnant for women who received levonorgestrel/ethinylestradiol pills or drospirenone/ethinylestradiol pills in these studies was also about 1 to 2% a year.

### VI.2.3 Unknowns Relating to Treatment Benefits

The development program for the etonogestrel/ethinylestradiol vaginal delivery system demonstrated that it was highly effective in preventing pregnancy.

## VI.2.4 Summary of Safety Concerns

## Important Identified Risks

## Table 1 Summary of Important Identified Risks

| Risk | What is Known | Preventability |
|---|---|---|
| Broken Ring | Very rarely etonogestrel/ethinylestradiol vaginal delivery system may break. | |
| Ring Slips Out | Etonogestrel/ethinylestradiol vaginal delivery system may accidentally slip out from the vagina- for example, if it has not been inserted properly, while removing a tampon, during sexual intercourse, during constipation, or if you have a prolapse of the womb. | |
| Unintended Pregnancies | Etonogestrel/ethinylestradiol vaginal delivery system is a vaginal birth control ring used to prevent pregnancy. It is intended for women of child- bearing age. Not every birth control method is 100% effective in every woman who uses it, even if she uses it correctly. Rarely pregnancy may occur. | If pregnancy occurs with etonogestrel/ethinylestradiol vaginal delivery system in the vagina, the ring should be removed. |
| Blood clots in a vein (referred to as 'venous thrombosis', 'venous thromboembolism' or VTE) | Using a combined hormonal contraceptive, such as etonogestrel/ethinylestradiol vaginal delivery system, increases your risk of developing a blood clot compared with not using one . In rare cases, a blood clot can block blood vessels and cause serious problems.<br>Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.<br>**It is important to remember that the overall risk of a harmful blood clot due to NuvaRing is small.**<br>**What can happen if a blood clot forms in a vein?**<br>• The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.<br>• If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).<br>• If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.<br>• Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis). | You should not use NuvaRing if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.<br>• if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs<br>• if you know you have a disorder affecting your blood clotting - for instance, protein C deficiency, protein S deficiency, antithrombin – III deficiency, Factor V Leiden or antiphospholipid antibodies<br>• if you need an operation or if you are off your feet for a long time (see section 'Blood clots')<br>• if you have ever had a heart attack, or a stroke<br>• if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms)<br>• if you have any of the following diseases that may increase your risk of a clot in the arteries: |

## Table 1 Summary of Important Identified Risks

| Risk | What is Known | Preventability |
|---|---|---|
| | **When is the risk of developing a blood clot in a vein highest?**<br>The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more.<br>After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.<br>When you stop using NuvaRing your risk of a blood clot returns to normal within a few weeks. | – severe diabetes with blood vessel damage<br>– very high blood pressure<br>– a very high level of fat in the blood (cholesterol or triglycerides)<br>– a condition known as hyperhomocysteinaemia<br>• if you have (or have ever had) a type of migraine called 'migraine with aura |
| Blood clots in a vein (referred to as 'venous thrombosis', 'venous thromboembolism' or VTE) | **What is the risk of developing a blood clot?**<br>The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are using.<br>The overall risk of a blood clot in the leg or lung (DVT or PE) with NuvaRing is small.<br>• Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.<br>• Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate, about 5-7 will develop a blood clot in a year.<br>• Out of 10,000 women who are using a combined hormonal contraceptive that contains norelgestromin, or etonogestrel such as NuvaRing, between about 6 and 12 women will develop a blood clot in a year.<br>• The risk of having a blood clot will vary according to your personal medical history (see "Factors that increase your risk of a blood clot" below).<br>**Factors that increase your risk of a blood clot in a vein**<br>The risk of a blood clot with NuvaRing is small but some conditions will increase the risk. Your risk is higher:<br>• if you are very overweight (body mass index (BMI) over 30 kg/m$^2$);<br>• if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g., below the age of about 50). In this case you could have a hereditary blood clotting disorder | If any of these conditions appear for the first time while using NuvaRing, remove the ring immediately and contact your doctor. In the meantime, use non-hormonal contraceptive measures. |

## Table 1 Summary of Important Identified Risks

| Risk | What is Known | Preventability |
|---|---|---|
| Blood clots in a vein (referred to as 'venous thrombosis', 'venous thromboembolism' or VTE) | • if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of NuvaRing may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop using NuvaRing ask your doctor when you can start using it again.<br>• as you get older (particularly above about 35 years)<br>• if you gave birth less than a few weeks ago<br>The risk of developing a blood clot increases the more conditions you have.<br>Air travel (>4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.<br>It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that NuvaRing needs to be stopped.<br>If any of the above conditions change while you are using NuvaRing, for example a close family member experiences a thrombosis for no known reason or you gain a lot of weight, tell your doctor. | |
| Blood clots in an artery | Like a blood clot in a vein, a blood clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.<br>**Factors that increase your risk of a blood clot in an artery**<br>It is important to note that the risk of a heart attack or stroke from using NuvaRing is very small but can increase:<br>• with increasing age (beyond about 35 years)<br>• **if you smoke.** When using a combined hormonal contraceptive, like NuvaRing, you are advised to stop smoking. If you are unable to stop smoking and are older than 35 your doctor may advise you to use a different type of contraceptive<br>• if you are overweight<br>• if you have high blood pressure<br>• if a member of your immediate family has had a heart attack or stroke at a young age (less than about 50). In this case you could also have a higher risk of having a heart attack or stroke.<br>• if you, or someone in your immediate family, have a high level of fat in the blood (cholesterol or triglycerides)<br>• if you get migraines, especially migraines with aura | You should not use NuvaRing if you have any of the conditions listed below. If you have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.<br>• if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs<br>• if you know you have a disorder affecting your blood clotting - for instance, protein C deficiency, protein S deficiency, antithrombin – III deficiency, Factor V Leiden or antiphospholipid antibodies<br>• if you need an operation or if you are off your feet for a long time (see section 'Blood clots')<br>• if you have ever had a heart attack, or a stroke<br>. |

## Table 1 Summary of Important Identified Risks

| Risk | What is Known | Preventability |
|---|---|---|
| Blood clots in an artery | • if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation)<br>• if you have diabetes<br>If you have more than one of these conditions or if any of them are particularly severe, the risk of developing a blood clot may be increased even more.<br>If any of the above conditions change while you are using NuvaRing, for example, you start smoking, a close family member experiences a thrombosis for no known reason, or you gain a lot of weight, tell your doctor. | • if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms)<br>• if you have any of the following diseases that may increase your risk of a clot in the arteries:<br>– severe diabetes with blood vessel damage<br>– very high blood pressure<br>– a very high level of fat in the blood (cholesterol or triglycerides)<br>– a condition known as hyperhomocysteinaemia<br>• if you have (or have ever had) a type of migraine called 'migraine with aura<br>If any of these conditions appear for the first time while using NuvaRing, remove the ring immediately and contact your doctor. In the meantime, use non-hormonal contraceptive measures |

## Important Potential Risks

## Table 2 Summary of Important Potential Risks

| Risk | What is Known |
|---|---|
| Toxic Shock Syndrome | Cases of toxic shock syndrome (TSS) have been associated with tampons and certain barrier birth control methods. Very rare cases of TSS have been reported by etonogestrel/ethinylestradiol vaginal delivery system users; in some cases the women also were using tampons. Use of the etonogestrel/ethinylestradiol vaginal delivery system has not been shown to cause TSS. |
| Vaginal Ring Site Tissue Overgrowth | In rare cases, the ring was found stuck to the lining of the vagina or became entrapped in the vaginal tissue that has grown over the ring and needed to be removed by a healthcare provider. |

**Missing Information (theoretical risks)**

**Table 3 Summary of Missing Information**

| Missing Information | What is Known |
|---|---|
| Endometrial Thickening | The number of reported endometrial thickening cases is very small in the context of the total number of etonogestrel/ethinylestradiol vaginal delivery systems sold. Use of the etonogestrel/ethinylestradiol vaginal delivery system has not been shown to cause endometrial thickening. |
| Pelvic Inflammatory Disease (infection of the female reproductive organs) | The number of reported cases of pelvic inflammatory disease is very small in the context of the total number of etonogestrel/ethinylestradiol vaginal delivery system sold. Use of the etonogestrel/ethinylestradiol vaginal delivery system has not been shown to cause pelvic inflammatory disease. |

## VI.3 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimization measures.

In addition, information to communicate the risk of blood clots has been provided in the first quarter of 2014 to physicians, pharmacists and other health care professionals through a DHPC.

The Summary of Product Characteristics and the Package Leaflet for etonogestrel/ethinylestradiol vaginal delivery system can be found in the product's EPAR page.

### VI.3.1 Planned Post-Authorization Development Plan

#### VI.3.1.1 List of Studies in Post-Authorization Development Plan

There are no studies in the post-authorization development plan for this medicine.

#### VI.3.1.2 Studies Which are a Condition of the Marketing Authorization

There are no studies in the post-authorization development plan for this medicine.

## VI.3.2 Summary of Changes to the Risk Management Plan Over Time

### Table 4 Major Changes to the Risk Management Plan

| RMP Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 27-Feb-2006 (at the time of authorization) | Important identified risks:<br>• Ring disconnection<br>• Ring expulsion<br>• Unintended pregnancies and their outcome<br>• Venous thromboembolic events<br>• Cerebrovascular events<br><br>Important potential risks:<br>• Toxic Shock Syndrome | |
| 2.0 | 10-Oct-2007 | Important identified risks:<br>• Ring disconnection<br>• Ring expulsion<br>• Unintended pregnancies and their outcome<br>• Venous thromboembolic events<br>• Cerebrovascular events<br>Important potential risks:<br>• Toxic Shock Syndrome<br>• Pelvic inflammatory disease<br>• Implant site fibrosis<br>• Endometrial hyperplasia | |
| 3.0 | 28-Jan-2009 | Important identified risks:<br>• Ring disconnection<br>• Ring expulsion<br>• Unintended pregnancy<br>• Venous thromboembolic events<br>• Cerebrovascular accidents<br>Important potential risks<br>• Toxic shock syndrome<br>• Implant site fibrosis<br><br>In this version endometrial hyperplasia and pelvic inflammatory disease (PID) were no longer considered potential risks and were not included in the RMP. | |
| 4.0 | 27-Aug-2010 | Important identified risks:<br>• Ring disconnection<br>• Ring expulsion<br>• Unintended pregnancy<br>• Venous thromboembolic events<br>• Cerebrovascular accidents<br><br>Important Potential Risks:<br>• Toxic shock syndrome<br>• Implant site fibrosis<br><br>Missing information:<br>• Endometrial hyperplasia<br>• Pelvic inflammatory disease<br><br>In this version endometrial hyperplasia and pelvic inflammatory disease (PID) are included as missing information based on a specific request of the EU health authority. | |

## Table 4 Major Changes to the Risk Management Plan

| RMP Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 5.0 | 25-July-2013 | Version 5.0 of the RMP incorporates information from a recently completed study, The Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) Study, conducted to describe and compare the risks of short- and long-term use of etonogestrel/ethinylestradiol vaginal delivery system with those of marketed combined oral birth control methods. No new risks or modifications to the existing risks have been added to the RMP as a result of this study. | |
| 6.0 | 28-April-2014 | A DHPC to communicate the risk of blood clots was implemented. The EU RMP and public summary was updated to reflect changes to the EU SmPC and patient leaflet. No new risks have been added to the RMP. | |
| 7.0 | 24-Jan-2017 | Important identified risks:<br>• Ring disconnection<br>• Ring expulsion<br>• Unintended pregnancy<br>• Venous thromboembolic events<br>• Cerebrovascular accidents<br><br>Important Potential Risks:<br>• Toxic shock syndrome<br>• Vaginal ring site tissue overgrowth<br><br>Missing information:<br>• Endometrial hyperplasia<br>• Pelvic inflammatory disease<br><br>In this version, the title of the Important potential risk of Implant site fibrosis was changed to Vaginal ring site tissue overgrowth and the description of the risk was updated to make it more consistent with the available data and to describe potential management options. No new risks have been added to this RMP. | |