VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The contraceptive vaginal ring is a relatively new combined hormonal contraceptive method. Ethinylestradiol and etonogestrel are rapidly absorbed through the vaginal epithelium and result in a steady serum concentration. Studies have demonstrated that the efficacy and safety of the ring are equivalent to oral contraceptives (OCs). Patients report being highly satisfied with the vaginal ring and report fewer systemic side effects than do OC users. The ring provides effective cycle control as well as symptom relief for women with menorrhagia, dysmenorrhea and polycystic ovarian syndrome.(2)

VI.2.2 Summary of treatment benefits

The findings from 1-year study of over 2,300 women in the United States, Canada and Europe show that combined contraceptive vaginal ring is an effective contraceptive that has exceptional cycle control, is well tolerated, and acceptable to most users. Good compliance with a contraceptive method is essential to maintain contraceptive reliability. It was observed that most women used the ring correctly and temporary ring removal rarely occurred. In 4.8% of cycles, the scheduled ring-free period was extended by more than 1 day, which may increase the risk of pregnancy.(3)

VI.2.3 Unknowns relating to treatment benefits

None identified.

VI.2.4 Summary of safety concerns

Table 27. Important identified risks

Important Identified Risk	What is known	Preventability
Ring disconnection	On very rare occasions it has been reported that the vaginal ring can get disconnected during use.	In order to ensure the efficacy, it is advised that the woman should regularly verify the presence and integrality of vaginal ring.
Ring expulsion	It has been reported, that the ring can get expelled, for example if the ring has not been inserted properly, while removing a tampon, during sexual intercourse, or in case of severe or chronic constipation. Prolonged expulsion may lead to contraceptive failure and/or breakthrough bleeding.	In order to ensure the efficacy, it is advised that the woman should regularly verify the presence of vaginal ring.
Unintended pregnancies	Studies have demonstrated that the efficacy of the ring is at least comparable to oral contraceptives (OCs).	Women should be instructed on how to use Etonogestrel / ethinylestradiol vaginal delivery system and respect the regimen of insertion and removal of the ring. They must

Important Identified Risk	What is known	Preventability
	The efficacy of Etonogestrel / ethinylestradiol 0.120/0.015 mg per 24 hours, vaginal delivery system may be reduced in the event of non-compliance.	be educated on what to do in case of deviations of the regimen: - what to do in case of a lengthened ring-free interval - what to do if the ring was temporarily outside the vagina - what to do in case of lengthened ring-use Users should inform the doctor about concomitant medication.
Blood clots in blood vessels which bring blood back to heart (venous thromboembolism)	CHCs should not be used in the presence of venous blood clots in the veins (deep venous thrombosis); or in the presence of a severe or multiple risk factor(s) such as diabetes mellitus with damaged blood vessels, very high blood pressure, and very high level of fat in the blood (cholesterol or triglycerides); hereditary or acquired increased risk of venous blood clots (thrombosis).	Etonorgestrel/ethinylestradiol should be prescribed with caution in patients with predisposing factors, and, if administered, an early detection and constant monitoring should be performed by the physician. Doctors should inform patients about risk factors and symptoms of blood clots in the veins, and should advise them to seek urgent medical attention in case symptoms appear A Patient Information Card and a Checklist for Prescribers would be distributed, according to National Authorities requirements, to remind risk factors and symptoms to Heatlhcare professionals and patients.
Blood clots in blood vessels which pump blood from heart (arterial thromboembolism)	CHCs should not be used in the presence of arterial blood clots in the veins (pulmonary embolism); or in the presence	Etonorgestrel/ethinylestradiol should be prescribed with caution in patients with predisposing factors, and, if

Important Identified Risk	What is known	Preventability
	of a severe or multiple risk factor(s) such as diabetes mellitus with damaged blood vessels, very high blood pressure, and very high level of fat in the blood (cholesterol or triglycerides); hereditary or acquired increased risk of arterial blood clots (thrombosis).	administered, an early detection and constant monitoring should be performed by the physician. Doctors should inform patients about risk factors and symptoms of blood clots in the arteries, and should advise them to seek urgent medical attention in case symptoms appear. A Patient Information Card and a Checklist for Prescribers would be distributed, according to National Authorities requirements, to remind risk factors and symptoms to Heatlhcare professionals and patients.

Table 28. Important potential risks

Important Potential Risk	What is known (including reason why it is considered a potential risk)
Potentially fatal illness caused by a bacterial toxin (toxic shock syndrome).	This condition may be associated with the use of tampons. Etonogestrel / ethinylestradiol vaginal delivery system, reference product, has not been shown to cause it.
Formation of excess connective tissue in a place of insertion (implant site fibrosis).	Very rarely it has been reported that the ring adhered to vaginal tissue, necessitating removal by a healthcare provider.

Table 29. Missing information

Missing Information	What is known
Excessive growth of the cells of the inner mucous membrane of the uterus (endometrial hyperplasia).	Etonogestrel / ethinylestradiol 0.12 mg/0.015 mg per 24 hours vaginal delivery system, reference product, has not been shown to cause endometrial hyperplasia

Missing Information	What is known
Infection of the upper part of the female reproductive system namely the uterus, fallopian tubes, and ovaries, and inside of the pelvis (pelvic inflammatory disease).	Etonogestrel / ethinylestradiol 0.12 mg/0.015 mg per 24 hours vaginal delivery system, reference product, has not been shown to cause pelvic inflammatory disease.

VI.2.5 Summary of risk minimisation 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 minimising 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 minimisation measures.

This medicine has additional risk minimisation measures.

The PRAC assessment report of the Article 31 referral EMEA/H/A-31/1356 for combined hormonal contraceptives, introduced additional risk minimisation measures with the aim to ensure safe and proper use of CHCs with respect to the increased risk of thrombosis (blood clots in veins and arteries) associated with the COCs in general.

These additional risk minimisation measures are for the following risks:

Venous thromboembolic events
Risk minimisation measure(s): Educational materials: Checklist for Prescribers and Patient Information Card.
Objective and rationale: Healthcare professionals and patients to understand the risk of blood clots in the veins and the appropriate management of this risk to minimise its occurrence and its severity.
Proposed action: - *Checklist for Prescribers* providing information on: o the increased risk of venous thromboembolism; o the risk factors of VTE o warning doctors to inform the patients about risk and symptoms of VTE o encouraging doctors to report adverse effects. - *Patient Information Card* providing information on: o special situations increasing risk of VTE o recognizing symptoms of VTE and seek immediate medical advice

Arterial thromboembolic events
Risk minimisation measure(s): Educational materials :Checklist for Prescribers and Patient Information Card
Objective and rationale: healthcare professionals and patients to understand the risk of blood clots in the ateries and the appropriate management of this risk to minimise its occurrence and its severity.
Proposed action: - *Checklist for Prescribers* providing information on: o the increased risk of venous thromboembolism; o the risk factors of ATE o warning doctors to inform the patients about risk and symptoms of ATE o encouraging doctors to report adverse effects. - *Patient Information Card* providing information on: o special situations increasing risk of ATE o recognizing symptoms of ATE and seek immediate medical advice

VI.2.6 Planned post-authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
01		*Identified Risks:* • Ring disconnection • Ring expulsion • Unintended pregnancies • Venous thromboembolic events • Arterial thromboembolic events *Potential Risks* • Toxic shock syndrome • Implant site fibrosis *Missing information* • Endometrial hyperplasia • Pelvic inflammatory disease	

Version	Date	Safety Concerns	Comment
02	12/02/2016	No changes are made in the safety concerns. Included as *additional risk minimisation measures a* Checklist for Prescribers and a Patient Information Card for the identified risks VTE and ATE.	
03	23/03/2017	No changes are made in the safety concerns	SmPC and PL are updated in Annex 2, as they have been modified on request of Health authorities.
04	11/05/2017	No changes are made in the safety concerns	Updated Annex 2 on request of HAs to include recent changes in Product Information of the reference product. Section SVII.4.2: deleted interaction with antibiotics (penicillins, tetracicylins) and added interaction between CHCs containing ethinylestradiol with products containing ombitasvir/paritaprevir/ritonavir and dasabuvir. F**or** safety concern "Unintended pregnancies", updated information on interactions (in 4.5 and 4.8) and posology (4.2) according to the updated SmPC, in tables **V.1. V.3 and VI.1.4**