

4 Part VI: Summary of activities in the risk management plan by product

4.1 Part VI.1 Elements for summary tables in the EPAR

Table 6-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Venous thromboembolic events Arterial thromboembolic events (incl. cardiovascular disease and stroke) Hepatobiliary disorders
Important potential risks	Effect on hereditary angioedema Pancreatitis (in patients with hypertriglyceridemia) Breast cancer Benign and malignant liver tumors Cervical cancer Crohn's disease and ulcerative colitis Insulin resistance/ decreased glucose tolerance Increase in blood pressure Worsening of depression
Missing information	None

Table 6-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

N/A

Table 6-3 Part VI.1.3 Summary of Post authorization efficacy development plan

N/A

Table 6-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Venous thromboembolic events	Guidance is provided in section 4.1 Therapeutic indications, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.6 Fertility, pregnancy and lactation, and section 4.8 Undesirable effects of the SmPC.	Distribution of: 1. Patient Information Card 2. Checklist for prescribers
Arterial thromboembolic events (incl. cardiovascular disease and stroke)	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	Distribution of: 1. Patient Information Card 2. Checklist for prescribers
Hepatobiliary disorders	Guidance is provided in sections 4.3 Contraindications, 4.4. Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects, and section 5.2 Pharmacokinetic properties of the SmPC.	None
Effect on hereditary angioedema	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Pancreatitis (in patients with hypertriglyceridemia)	Guidance is provided in sections 4.4 Special warnings and precautions for use and 4.8. Undesirable effects of the SmPC.	None
Breast cancer	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Benign and malignant liver tumors	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Cervical cancer	Guidance is provided in section 4.3 Contraindications and section 4.4 Special warnings and precautions for use of the SmPC.	None
Crohn's disease and ulcerative colitis	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None
Insulin resistance/ decreased glucose tolerance	Guidance is provided in section 4.3 Contraindications and section 4.4 Special warnings and precautions for use of the SmPC.	None

Increases in blood pressure	Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, and section 4.8 Undesirable effects of the SmPC.	None
Hyperkalemia	Guidance is provided in section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction and section 5.2 Pharmacokinetic properties of the SmPC.	None
Worsening of depression	Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC.	None

4.2 Part VI.2 Elements for a Public Summary

4.2.1 Part VI.2.1 Overview of disease epidemiology

Globally, 63% of married women or those in union were using some form of contraception in 2008. However, in the WHO African Region, use of contraceptive was below 25% and 43% in the WHO Eastern Mediterranean Region [\[WHO, 2013\]](#). In 2012, 70.7% of European married women or those in union were using some form of contraception [\[WHO, 2012\]](#). Globally, 10% of women were found to use combined hormonal contraceptives. Women in developed countries (16%) use a higher proportion of these drugs than the women in developing countries (6%) [\[IARC\]](#).

Today, the voluntary control of fertility is of paramount importance to modern society. From a global perspective, countries currently face the crisis of rapid population growth that has begun to threaten human survival. On a smaller scale, effective birth control can be essential to a woman's ability to achieve her individual goals and to contribute to her sense of well-being [\[Medscape, 2013\]](#).

4.2.2 Part VI.2.2 Summary of treatment benefits

There are several contraceptive methods available. Examples are oral, injectable or implantable hormonal contraceptives, intrauterine devices, condoms, male or female sterilization, periodic abstinence, or spermicidal agents. A patient's choice of contraceptive method involves factors such as efficacy, safety, non-contraceptive benefits, cost, and personal considerations [\[Medscape, 2013\]](#).

With 30%, oral contraceptives like ethinylestradiol/drospirenone are the most widely used method of contraception for women in Europe. This is followed by condom use (20%), reversible long-term contraceptive methods (11%), sterilization methods (11%), and unreliable methods of contraception (6%) [\[Skouby S, 2010\]](#). Failure rates of oral contraceptives are correlated to individual compliance and range from 0.1-0.3% with perfect use to 2.2 - 8% with typical use [\[Medscape, 2013\]](#) [\[Wiegratz I, 2011\]](#).

4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Unaware of any evidence suggesting that efficacy is reduced or enhanced in any target subpopulations.

4.2.4 Part VI.2.4 Summary of safety concerns

Table 6-5 Important identified risks

Risk	What is known	Preventability
<p>Blood clots of a vein (Venous thromboembolic events)</p>	<p>The use of any (COC) carries an increased risk of VTE compared with no use.</p> <p>There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.</p> <p>The excess risk of VTE is highest during the first year a woman ever uses a COC. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. Occurrence of VTE is rare.</p> <p>Signs and symptoms of formation of a blood clot within a deep vein, predominantly in the legs (deep vein thrombosis) include:</p> <ul style="list-style-type: none"> • swelling of one leg or along a vein in the leg or foot especially when accompanied by: • pain or tenderness in the leg which may be felt only when standing or walking • increased warmth in the affected leg • change in color of the skin on the leg e.g. turning pale, red or blue <p>Symptoms of blood clot in the eye (retinal vein thrombosis) include:</p> <ul style="list-style-type: none"> • immediate loss of vision or painless blurring of vision which can progress to loss of vision 	<p>COCs should not be used in the presence of blood clot in veins (venous thrombosis) present or in history blood clot in a vein deep inside a part of the body (deep venous thrombosis).</p> <p>Seek Urgent medical attention if you notice any of the mentioned signs or symptoms</p> <p>If a hereditary tendency is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.</p> <p>It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of ethinylestradiol/drospirenone compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.</p> <p>The product should be stopped when venous thrombosis appears for the first time during COC use.</p>

<p>Blood clots of an artery (Arterial thromboembolic events (incl. cardiovascular disease and stroke))</p>	<p>Studies have associated the use of combined COCs with an increased risk for heart reported to occur in liver (hepatic), bowel (mesenteric), kidney (renal) or eye (retinal)</p> <p>Signs and symptoms of blockage in one of the pulmonary arteries in lungs (pulmonary embolism) and heart attack include:</p> <ul style="list-style-type: none"> • sudden unexplained breathlessness or rapid breathing; • sudden cough without an obvious cause, which may bring up blood; • sharp chest pain which may increase with deep breathing; • severe light headedness or dizziness; • rapid or irregular heartbeat • severe pain in your stomach; • upper body discomfort radiating to the back, jaw, throat, arm and stomach • sweating, nausea, vomiting <p>Signs and symptoms of Stroke include:</p> <ul style="list-style-type: none"> • sudden weakness or numbness of the face, arm or leg, especially on one side of the body; • sudden confusion, trouble speaking or understanding; • sudden trouble seeing in one or both eyes; • sudden trouble walking, dizziness, loss of balance or coordination; • sudden, severe or prolonged headache with no known cause; • loss of consciousness or fainting with or without seizure. 	<p>COCs should not be used in the presence of arterial thrombosis present or in history.</p> <p>Urgent medical attention if you notice any of the mentioned signs or symptoms</p> <p>It is important to draw a woman's attention to the information on arterial thrombosis, including the risk of ethinylestradiol/drospirenone compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.</p> <p>Should arterial thrombosis, prodromal conditions or blood flow to a part of your brain is stopped either by a blockage or a rupture of a blood vessel (cerebrovascular accident) appear for the first time during COC use, the product should be stopped. If you are unsure about the mentioned signs and symptoms, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').</p> <p>Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.</p>
<p>Disorders in liver and gallbladder (Hepatobiliary disorders)</p>	<p>Signs and symptoms include abnormal laboratory values, jaundice, pruritus, nausea, vomiting and diarrhea.</p>	<p>You should not use combination birth control pills if you have a disease of the liver and gallbladder.</p> <p>If the laboratory tests for liver and bile are abnormal then the use of combination birth control pills should be discontinued until it return to normal.</p>

Table 6-6 Important potential risks

Risk	What is known
Increase of swelling of the deeper layers of	Sudden swelling of the skin and/or mucous

Risk	What is known
the skin, caused by a build-up of fluid (Effect of hereditary angioedema)	membranes (e.g. tongue or throat), and/or difficulty swallowing or rashes (hives) together with difficulty breathing (angioedema) may occur in women taking combination birth control pills. You should see your doctor immediately if you experience symptoms of angioedema.
Inflammation of the pancreas (pancreatitis) in patients with elevated levels of fat in the blood (hypertriglyceridemia) (Pancreatitis (in patients with hypertriglyceridemia))	Patients with hypertriglyceridemia may be at an increased risk of pancreatitis when using COCs. COCs should not be used in the presence of pancreatitis or history of such a condition, if associated with severe hypertriglyceridemia. Should pancreatitis appear for the first time during COC use, the product should be stopped. In some situations you need to take special care while using ethinylestradiol/drospirenone or any other combination pill, and your doctor may need to examine you regularly like if you have elevated levels of fat in the blood (hypertriglyceridemia) or a positive family history for this condition. If the condition develops, or gets worse while you are using ethinylestradiol/drospirenone, you should also tell your doctor.
Breast cancer	The frequency of diagnosis of breast cancer is very slightly increased among OC users. Tell your doctor if a close relative has or has ever had breast cancer so that may examine you regularly. COCs should not be used in the presence of known or suspected breast cancer.
Benign and malignant liver tumors	In rare cases, benign liver tumours, and in even fewer cases malignant liver tumors have been reported in pill users. COCs should not be used in the presence or history of liver tumors (benign or malignant). Should a liver tumor appear for the first time during COC use, the product should be stopped. Contact your doctor if you have unusually severe abdominal pain.
Cervical cancer	An increased risk of cervical cancer in long-term users of COCs has been reported in some studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behavior and other factors such as human papilloma virus. COCs should not be used in the presence of known or suspected cervical cancer.
Chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis)	Chronic inflammatory bowel diseases have been reported during COC use, However, the association with COC use is not conclusive. The patients with inflammatory bowel disease should be excluded. Tell your doctor if you have chronic inflammatory bowel disease.
Inability to control blood sugar (Insulin resistance/ decreased glucose tolerance)	The use of combination birth control pills in diabetic women can cause difficulty in controlling the blood sugar in such patients. It is important to note that the risk of a heart attack or stroke from using ethinylestradiol and drospirenone is very small but

Risk	What is known
	can increase if you have diabetes. Tell your doctor if you have diabetes prior to starting therapy with combination birth control pills.
Increase in blood pressure	It is important to note that the risk of a heart attack or stroke from using ethinylestradiol/drospirenone is very small but can increase if you have high blood pressure. One of the uncommon side effects of ethinylestradiol/drospirenone is high blood pressure.
Increase potassium level (Hyperkalemia)	The potassium-sparing effect of ethinylestradiol/drospirenone may interfere with other drugs possibly inducing hyperkalemia. The serum potassium levels should be monitored under the combined use of ethinylestradiol/drospirenone and potassium-sparing drugs.
Worsening of depression	Depressive mood has been reported to occur or deteriorate during both pregnancy and COC use, but the evidence of an association with COC use is inconclusive. Depressed mood is observed commonly with COC use. If you experience any mood swings, feelings of sadness, loss, frequently in your daily life talk your doctor or pharmacist.

Table 6-7 Missing information

Risk	What is known
None	N/A

4.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a 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.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures). These additional risk minimization measures are for the following risks:

Risk minimization measure(s)

Summary description of main additional risk minimization measures:

Emboic and thrombotic events (Venous thromboembolic events and Arterial thromboembolic events (incl. cardiovascular disease and stroke))

Objective and rationale: To remind HCPs of the importance of recognizing the risk of a blood clot occurrence and the need to instruct patients on correct identification of signs and symptoms they need to look out for and what action are needed to be taken.

Proposed action:

DHPC

The PRAC requested a DHPC to be communicated, following the changes of the label. This was sent to the HCPs as requested.

The Patient Information Card

The Patient Information Card is instructing the patients:

- In which situations is the risk of a blood clot highest
- When to immediately seek medical attention

Risk minimization measure(s)

- What symptoms need to be addressed towards the care giver
- When should the patients inform the doctor, nurse or surgeon that she is taking Drospirenone/Ethinylestradiol.

The Checklist for Prescribers

The Checklist for Prescribers encourages the HCPs to use this tool in conjunction with the Summary of Product Characteristics during every combined hormonal contraceptive (CHC) consultation. The HCPs are advised for which medical conditions the CHC should not be used and the HCPs are advised to discuss the suitability of a CHC with the patient. The patients should be informed about the situations when the blood clot risk is increased.

4.2.6 Part VI.2.6 Planned post authorization development plan

None

4.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first version.