Risk Management Plan

Active substance: Drospirenone/ethinylestradiol

Version number: 4.0

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Oral contraception

Effective control of reproduction can be essential to a woman's ability to achieve her individual goals and to contribute to her sense of well-being. A patient's choice of contraceptive method involves factors such as efficacy, safety, noncontraceptive benefits, cost, and personal considerations.[1]

In 2009 the mean global percentage using contraception in women who are married or in union was 62.7%. COC represented 8.8% of contraceptive prevalence, reaching 15.4% in more developed countries. More than 100 million women worldwide use COCs. However, each year, many unintended pregnancies occur, indicating the importance of contraception.[2]

VI.2.2 Summary of treatment benefits

Birth control pills today are designed to improve safety and reduce side effects. Lower doses of estrogen lead to fewer side effects, such as weight gain, painful breasts, and feeling sick. The pills prevent ovulation (release of an egg) and so prevent pregnancy.[3]

The efficacy of this medicine is presented in two studies involving 1990 women. Only thirteen pregnancies were reported.[4]

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, taking into account factors such as age, sex, and race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Blood clots in the veins (ve-	This type of contraceptive is	Yes, by not allowing COCs to

Risk	What is known	Preventability
nous thromboembolic events/VTE)	known as a combined oral contraceptive (COC). The use of any COC increases the risk of blood clots in veins (venous thromboembolism/VTE). The risk is highest during the first year of use. The risk of blood clots in veins in COC users increases with age, family history, when not moving for a long time, when overweight.	be used by patients at risk of vein problems. Doctors should think about prescribing medicines that make the blood less likely to clot. If showing signs of a possible blood clot, COC users should be told to contact their doctor. If a blood clot is suspected or confirmed, COC use should be stopped.
Blood clots in the arteries (arterial thromboembolic events (incl. cardiovascular disease and stroke)/ATE)	Studies have shown that use of COCs may increase the risk of arterial blood clots (heart attack, transient ischaemic attack). The risk of arterial blood clots in COC users increases with age, smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC), high blood pressure, migraine, when overweight, family history (arterial blood clot in a sibling or parent at a relatively early age), disease of the valves of the heart, irregular heart and pulse rate.	Yes, by not allowing COCs to be used by patients at risk of arterial disease. Doctors should think about prescribing medicines that make the blood less likely to clot. If showing signs of a possible blood clot, COC users should be told to contact their doctor. If a blood clot is suspected or confirmed, COC use should be stopped.
Liver disorders (Hepatobiliary disorders)	Disturbances of liver function may mean that use of COCs should be stopped until liver function returns to normal.	There is no specific measure to prevent the occurrence of disturbances of liver function. The risk can be reduced by not allowing COCs to be used by patients with presence or history of severe liver disease as long as liver function has not returned to normal.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Worsening of depression	Worsening of depression has been reported during COC use.

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	This is considered a potential risk because treatment with COCs may cause depression as a side-effect.
Crohn's disease (inflammation, thickening and ulceration of the intestines) and ulcerative colitis (ulcers and inflammation of the colon)	Worsening of Crohn's disease and of ulcerative colitis has been reported during COC use.
Effect on a particular inherited serious allergic reaction characterised by swelling of body parts (Effect on hereditary angioedema)	In women with inherited serious allergic reaction (swelling of the face, throat or tongue) the use of COCs may cause or increase these events.
Inflammation of the pancreas (Pancreatitis (in patients with hypertriglyceridemia))	Women with presence or history of high cholesterol levels (hypertriglyceridemia) may be at an increased risk of inflammation of the pancreas when using COCs.
Breast cancer	Studies have shown that there is a slightly increased risk of breast cancer in women who are using COCs. The risk gradually disappears during the 10 years after stopping COC use. These studies do not provide evidence that COCs cause breast cancer.
Non-cancerous and cancerous liver tumours (Benign and malign liver tumours)	In rare cases, non-cancerous liver tumours, and even more rarely, cancerous liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening bleeding inside the abdomen. A liver tumour should be considered as a possibility when severe upper abdominal pain, liver enlargement or signs of bleeding inside the abdomen occur in women taking COCs.
Cancer of the neck of the uterus (cervix) Cervical cancer	Some studies have shown an increased risk of cervical cancer in long-term users of COCs, but the cause of this increased risk has not been agreed.
Increased blood pressure	Small increases in blood pressure have been reported in many women taking COCs. However, serious increases are rare. Only in these rare cases should COC use be stopped immediately. Where considered appropriate, COC use may be resumed if normal blood pressure can be achieved with blood pressure lowering therapy.
Condition in which cells fail to respond to the normal actions of the hormone insulin (Insulin resistance/decreased glucose tolerance)	COCs may affect the actions of the hormone insulin (a hormone produced in the pancreas that regulates the amount of glucose in the blood). This is considered a potential risk because treatment with COCs may influence the cells in the body to become resistant to insulin and reduce their ability to use insulin effectively by altering the use of the sugar in the body.

Risk	What is known (Including reason why it is considered a potential risk)
High levels of blood potassium (Hyperkalaemia)	COCs may increase the levels of blood potassium which can cause abnormal heart rhythm.

Missing information

Risk	What is known
NA	NA

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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Blood clots in the veins (venous thromboembolism) and blood clots in the arteries (arterial thromboembolism)

Healthcare Professional Communication and patient education
Objective and rationale The Direct Healthcare Professional Communication (DHPC) and the educational materials were needed to provide an update to the prescribing advice for CHCs, in order to ensure that the HCPs and/or patients are aware of the differences in the risk of venous and arterial thromboembolism between products, the importance of individual risk factors and to reinforce the importance of remaining vigilant for signs and symptoms.
Proposed action: Mandatory: 1. DHCP to be provided to all prescribers of contraception and any healthcare professional that may be faced with a possible thromboembolism due to CHCs. Optional: 2. Doctors Guide: Prescriber checklist* 3. Patient Guide: User card* 4. Patient Guide: Information sheet*

* Educational material at points 2.-4. may be optionally used according to national competent authorities requirements.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for drospirenone/ ethinylestradiol.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	12-10-2012	**Important identified risks**: -Risk of venous thromboembolism -Breast cancer **Important potential risks**: -Tumours: Cervical cancer, Liver tumours	Initial version
2.0	29-04-2013	Arterial thromboembolism, disturbances of liver function, pancreatitis, increased blood pressure, effect on hereditary angioedema, were added as **important identified risks**. Cervical cancer and liver tumours were changed from **important potential risks to important identified risks.** Worsening of endogenous depression and worsening of Crohn's disease and ulcerative colitis were added as **important potential risks.**	New important identified risks and important potential risks were included.
2.1	29-05-2013	Non safety related update: new product added	2.1
3.0	19-05-2015	No changes regarding the list of safety concerns Additional RMMs for the risks of venous and arterial thromboembolism are introduced in order to to reflect the EC decision for CoC Article 31 referral regarding the risk of thromboembolic events. Deletion of two products: Cléodette (National, FR) Cléosenza (National, FR)	NA
4.0	11-09-2015	Insulin resistance/decrease glucose tolerance and Hyperkalaemia were added as **important potential risks.** Six risks namely, Venous thromboembolism, Arterial thromboembolism, Disturbances of liver function, Pancreatitis, Worsening of endogenous depression and	Two new safety concerns were included in order to be in line with the originator's risks. Some risks have been

Version	Date	Safety Concerns	Comment
		Worsening of Crohn's disease and ulcerative colitis were renamed Venous thromboembolic events, Arterial thromboembolic events (incl. cardiovascular disease and stroke), Hepatobiliary disorders, Pancreatitis (in patients with hypertriglyceridemia), Worsening of depression and Crohn's disease and ulcerative colitis. Breast cancer, Effect on hereditary angioedema, Pancreatitis (in patients with hypertriglyceridemia), Benign and malign liver tumours, Cervical cancer and Increased blood pressure were moved from **important identified risks** to **important potential risks.**	renamed and some safety concerns have been moved from important identified risks to important potential risks.