

Summary of activities in the risk management plan by product - Levonorgestrel/ethinylestradiol 150/30 mcg Exeltis

Via.2 Elements for a public summary

Via.2.1 Overview of disease epidemiology

Oral contraception

Oral contraception is one of the most widely used medications and its safety has been investigated in thousands of epidemiological studies.(3) Nearly four million women in the UK, and 60 million women worldwide, now use the pill as a convenient and effective way to control their fertility. If taken correctly, the pill has a 99% annual effectiveness.

Between 30% and 40% of women of childbearing age use oral contraceptives and about 30% of these use the newer oral contraceptives. Approximately 1.5 million women were using third- generation oral contraceptives in the UK alone.(1)

A report, based on up to 25 years of follow-up, suggested that most of the mortality effects of oral contraceptives occurred in current or recent users, with few effects persisting beyond 10 years after stopping use.(4) A publication from the large contraception study using incident cancer data suggested that ever users of oral contraceptives may have a reduced overall risk of cancer.(5)

Via.2.2 Summary of treatment benefits

Hormonal contraceptives are among the most popular, safe, and effective methods of reversible contraception. Authorities all over the world – including the US Food and Drug Administration and the European Medicines Agency – stipulate assessment of efficacy by the Pearl Index (PI).(6)

A Pearl Index is a formula that allows comparison of the efficacy of contraceptive methods, calculated as the pregnancy rate in population divided by 100 years of user exposure.(7)

The minimum value of the index is 0 (no unscheduled pregnant woman), the maximum is not 100, but 1200 (or 1300), in the case where all women in the study became pregnant immediately during the first month (or menstrual cycle).(8)

As stated in the SmPC- overall Pearl Index (method failure + patient failure): 0.59 (upper tow- sided 95% confidence limit: 0.85).

Via.2.3 Unknowns relating to treatment benefits

None identified.

Via.2.4 Summary of safety concerns

Table 32. Important identified risks

Important Identified Risk	What is known	Preventability
Blood clots in blood vessels which bring blood back to heart (venous thromboembolism)	COCs 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).	Levonorgestrel / 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.
Blood clots in blood vessels which pump blood from heart (arterial thromboembolism)	COCs should not be used in the presence of arterial blood clots in the veins (pulmonary embolism); or in the presence of a severe or multiple risk factor(s) such as	Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors, and, if administered, an early detection

Important Identified Risk	What is known	Preventability
	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).	and constant monitoring should be performed by the physician.
Benign and malignant liver tumours	In rare cases, benign, and even more rarely, malignant liver tumours have been reported in COC users. In isolated cases, these tumours have led to life-threatening bleeding inside the stomach. The possibility of a liver tumour should be considered in the differential diagnosis of women taking COCs who report severe upper stomach pain, liver enlargement or signs of bleeding inside the stomach.	Levonorgestrel / 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.

Breast cancer	The frequency of diagnosis of breast cancer is slightly increased among COC users, but it is not known whether this is caused by the treatment. As breast cancer is rare in women under 40 years of age, the excess number is small in relation to the overall risk of breast cancer. COCs should not be used in case of known or suspected sex-steroid influenced cancer (e.g. breast cancer).	Levonorgestrel / 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.
Disturbances of liver function	Disturbances of liver function have been reported in COC users. COCs should not be used in case of current liver tumours or history of liver tumours (benign or malignant).	Physician will monitor the liver functions and may decide to discontinue the drug if needed.
Inflammation of pancreas (pancreatitis)	Women with elevated levels of fat in the blood (hypertriglyceridemia), or a positive family history for this condition, may be at an increased risk of inflammation of the pancreas (pancreatitis) when using COCs.	Levonorgestrel / 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.
Effect on hereditary serious allergic reaction which causes swelling of the face or throat (angioedema)	In women with hereditary serious allergic reaction which causes swelling of the face or throat, exogenous estrogens can trigger worsening of these symptoms.	Levonorgestrel / 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.

Table 33. Important potential risks

Important Potential Risk	What is known (including reason why it is considered a potential risk)
Cancer of genital organs (cervical cancer)	Some epidemiological studies have reported an increased risk of cancer of the genital organs (cervical cancer) in long-term COC users. OCs should not be used in case of known or suspected sex-steroid influenced cancer (e.g. of the genital organs).
Worsening of endogenous depression	Worsening of depression (endogenous depression) has been reported during COC use. Depressed mood and mood altered have been observed with the use of combined oral contraceptives containing levonorgestrel / ethinylestradiol.

Worsening of inflammatory bowel diseases (worsening of Crohn’s disease and ulcerative colitis)	Worsening of inflammatory bowel disease (Crohn’s disease and of ulcerative colitis) has been reported during COC use. Inflammatory bowel diseases (Crohn’s disease and ulcerative colitis) have been reported in women using COC.
Increased blood pressure	Although small increases in blood pressure have been observed in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in pre-existing high blood pressure, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to treatment with blood pressure medicine, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normal values can be achieved with blood pressure medicine.
Insulin resistance/decreased glucose tolerance	Although COCs may have an effect on peripheral insulin resistance and glucose tolerance there is no

Important Potential Risk	What is known (including reason why it is considered a potential risk)
	evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

Table 34. Missing information

Missing Information	What is known
None.	

Via.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 no additional risk minimisation measures.

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

Not applicable.

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

Not applicable.