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

## VIa.1 Elements for summary tables in the EPAR

Please note that Levonorgestrel/ethinylestradiol 150/30 mcg are different brand names of the same medicinal product with the identical SmPC, with slightly difference within the posology part only. As the safety concerns and their management including planned pharmacovigilance activities, as well as indications, target population and other information are identical for two products covered by this RMP, the information in Part VIa is presented only once together for these two products.

### *VIa.1.1 Summary table of Safety concerns*

Summary table of safety concerns

| | |
|---|---|
| **Important identified risks** | • Venous thromboembolism<br>• Arterial thromboembolism<br>• Benign and malignant liver tumours<br>• Breast cancer<br>• Disturbances of liver function<br>• Pancreatitis<br>• Effect on hereditary angioedema |
| **Important potential risks** | • Cervical cancer<br>• Worsening of endogenous depression<br>• Worsening of Crohn's disease and ulcerative colitis<br>• Increased blood pressure<br>• Insulin resistance/decreased glucose tolerance |
| **Missing information** | None identified |

### *VIa.1.2 Table of on-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan (if applicable)*

Not applicable.

### *VIa.1.3 Summary of Post-authorisation efficacy development plan (if applicable)*

Not applicable.

### *VIa.1.4 Summary table of risk minimisation measures*

Summary table of risk minimisation measures

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Venous thromboembolism | Warning in section 4.1<br>Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Mentioned in fertility pregnancy and lactation in section 4.6<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Arterial thromboembolism | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Benign and malignant liver tumours | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Breast cancer | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Information in section 5.3.<br>Prescription only medicine. | Not applicable. |
| Disturbances of liver function | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Interaction in section 4.5<br>Prescription only medicine. | Not applicable. |
| Pancreatitis | Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |
| Effect on hereditary angioedema | Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |
| Cervical cancer | Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Worsening of endogenous depression | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Worsening of Crohn's disease and ulcerative colitis | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Increased blood pressure | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Insulin resistance/decreased glucose tolerance | Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |

## 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*

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 diabetes mellitus with damaged | Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors, and, if administered, an early detection and constant |

| Important Identified Risk | What is known | Preventability |
|---|---|---|
| | 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). | 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 sever 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.<br>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.<br>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 | 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. |

| Important Identified Risk | What is known | Preventability |
|---|---|---|
| | pancreas (pancreatitis) when using COCs. | |
| 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. |

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.<br>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.<br>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.<br>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 evidence for a need to alter the therapeutic regimen in |

| Important Potential Risk | What is known (including reason why it is considered a potential risk) |
|---|---|
| | 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. |

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.

# PART VIb Summary of activities in the risk management plan by product - Levonorgestrel/Ethinylestradiol 100/20 mcg

Please note that Levonorgestrel/ethinylestradiol 100/20 mcg are different brand names of the same medicinal product with the identical SmPC, with slightly different posology only. As the safety concerns and their management including planned pharmacovigilance activities, as well as indications, target population and other information are identical for two products covered by this RMP, the information in Part VIb is presented only once together for these two products.

## VIb.1 Elements for summary tables in the EPAR

### *VIb.1.1 Summary table of Safety concerns*

Summary table of safety concerns

| | |
|---|---|
| **Important identified risks** | • Venous thromboembolism<br>• Arterial thromboembolism<br>• Benign and malignant liver tumours<br>• Breast cancer<br>• Disturbances of liver function<br>• Pancreatitis<br>• Effect on hereditary angioedema |
| **Important potential risks** | • Cervical cancer<br>• Worsening of endogenous depression<br>• Worsening of Crohn's disease and ulcerative colitis<br>• Increased blood pressure<br>• Insulin resistance/decreased glucose tolerance |
| **Missing information** | None identified |

### *VIb.1.2 Table of on-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan (if applicable)*

Not applicable.

### *VIb.1.3 Summary of Post-authorisation efficacy development plan (if applicable)*

Not applicable.

### *VIb.1.4 Summary table of risk minimisation measures*

Summary table of risk minimisation measures

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Venous thromboembolism | Warning in section 4.1<br>Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Mentioned in fertility pregnancy and lactation in section 4.6<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Arterial thromboembolism | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Benign and malignant liver tumours | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Breast cancer | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Information in section 5.3.<br>Prescription only medicine. | Not applicable. |
| Disturbances of liver function | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Interaction in section 4.5<br>Prescription only medicine. | Not applicable. |
| Pancreatitis | Contraindicated in section 4.3.<br>Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |
| Effect on hereditary angioedema | Warning in section 4.4.<br>Prescription only medicine. | Not applicable. |
| Cervical cancer | Warning in section 4.4. | Not applicable. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Prescription only medicine. | |
| Worsening of endogenous depression | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Worsening of Crohn's disease and ulcerative colitis | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Increased blood pressure | Warning in section 4.4.<br>Listed among undesirable effects in section 4.8.<br>Prescription only medicine. | Not applicable. |
| Insulin resistance/decreased glucose tolerance | Warning in section 4.4.<br>Prescription only medicine. | Not applicable |

## VIb.2 Elements for a public summary

### *VIb.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)

### *VIb.2.2 Summary of treatment benefits*

The efficacy of the 100 µg levonorgestrel and 20 µg ethinyl estradiol on inhibition of the ovarian activity has been confirmed by different well-designed studies performed during years.

In one of them, 24 healthy women between 20 and 34 years old, with normal ovulatory cycles and not at risk for becoming pregnant took 1 tablet of active drug. The diameter of ovarian follicles and the level of estrogens have been measured before, during and after the treatment.

The results showed that mean levels of estrogens remained suppressed during the treatment. No escape ovulation was observed during the treatment phase of the study and there were no pregnancies. Ovulation was noted to return rapidly in the post treatment cycle. Results indicate that the oral contraceptive containing 100 µg levonorgestrel combined with 20 µg ethinylestradiol effectively inhibits ovulation, providing adequate suppression of ovarian activity.(9)

### *VIb.2.3 Unknowns relating to treatment benefits*

None identified.

### *VIb.2.4 Summary of safety concerns*

Important identified risks

| **Important Identified Risk** | **What is known** | **Preventability** |
|---|---|---|
| Blood clots in blood vessels which bring blood back to heart (venous thromboembolism) | Combined Oral Contraceptives (COC) 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 | Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors, and, if administered, an |

| Important Identified Risk | What is known | Preventability |
|---|---|---|
| | 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). | early detection 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 sever 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.<br>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.<br>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 | Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors and, if administered, an early detection and constant |

| Important Identified Risk | What is known | Preventability |
|---|---|---|
| | pancreas (pancreatitis) when using COCs. | 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. |

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.<br>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.<br>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.<br>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. |

Missing information

| Missing Information | What is known |
|---|---|
| None. | |

### *VIb.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.

### *VIb.2.6 Planned post-authorisation development plan (if applicable)*

Not applicable.

### *VIb.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 |
|---|---|---|---|
| 01 | July 2015 | Identified Risks<br>• Venous thromboembolism<br>• Arterial thromboembolism<br>• Benign and malignant liver tumours<br>• Breast cancer<br>• Disturbances of liver function<br>• Pancreatitis<br>• Increases in blood pressure<br>• Effect on hereditary angioedema<br>Potential Risks<br>• Cervical cancer<br>• Worsening of endogenous depression | |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | • Worsening of Crohn's disease and ulcerative colitis<br>Missing information<br>None | |
| 02 | 17 Jan 2017 | Identified Risks<br>• Venous thromboembolism<br>• Arterial thromboembolism<br>• Benign and malignant liver tumours<br>• Breast cancer<br>• Disturbances of liver function<br>• Pancreatitis<br>• Effect on hereditary angioedema<br>Potential Risks<br>• Cervical cancer<br>• Worsening of endogenous depression<br>• Worsening of Crohn's disease and ulcerative colitis<br>• Increased blood pressure Insulin resistance / decreased glucose tolerance<br>Missing information<br>None<br>On suggestion by Health Authority, Increased blood pressure is moved to important potential risk and Insulin resistance/decreased glucose tolerance is added as important potential risk. | |
| 03 | 09 May 2017 | No changes were made in safety concerns | The RMP is updated to include changes in SmPC requested by HAs during the registration procedure. It concerns to interaction with CHCs containing ethinylestradiol and ombitasvir/ paritaprevir/ ritonavir. Updated sections SVII.4 of RMP<br>Also, included in 4.1 warning on VTE. Updated tables regarding Risk minimisaton measures in section V and VI including this warning for the safety concern "Venous |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | | thromboembolism".<br><br>Annex 2 is updated |
| 4.0 | 13 Nov 2017 | Module SV Post-authorisation experience was amended. Annex 2 was changed (relevant SmPCs/PILs were attached) and annex 3 was amended.<br><br>No changes were made to safety concerns. | This RMP update is prepared for the renewal submission. Module SV Post-authorisation experience, Annex 2 and Annex 3 were amended. |

Not applicable.