Part VI: Summary of the risk management plan

Summary of risk management plan for Lydisilka

This is a summary of the risk management plan (RMP) for Lydisilka. The RMP details important risks of Lydisilka, how these risks can be minimized, and how more information will be obtained about Lydisilka's risks and uncertainties (missing information).

Lydisilka's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Lydisilka should be used.

This summary of the RMP for Lydisilka should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lydisilka's RMP.

I. The medicine and what it is used for

Lydisilka is authorized for oral contraception. It contains estetrol and drospirenone as the active substances.

Further information about the evaluation of Lydisilka's benefits can be found in Lydisilka's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/lydisilka

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Lydisilka, together with measures to minimize such risks and the proposed studies for learning more about Lydisilka's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Lydisilka, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lydisilka is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lydisilka are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lydisilka. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Venous thromboembolism
	Arterial thromboembolism
Important potential risks	None
Missing information	Exposure during pregnancy

II.B Summary of important risks

Identified risk: Venous thromboembolism (VTE)	
Evidence for linking the risk to the medicine	The increased risk of VTE (blood clots in the veins) in women taking combined oral contraceptives (COCs) has been known for many years and is very small. The risk of blood clots in the veins varies between COCs, depending on the dose of estrogen and on the type of progestin (a hormone) they contain, and ranges from 5 to 12 cases of blood clots per 10,000 women who use them for a year. This compares with 2 cases of blood clots in the veins each year per 10,000 women who are not using COCs. Blood clots in the veins of the legs may lead to a painful swelling of the legs (deep vein thrombosis [DVT]) and very occasionally to life threatening or fatal events if the clots are dislodged and travel to the lungs (pulmonary embolism [PE]). In clinical studies investigating the recommended dose of Lydisilka in 3790 women, there was one report of deep venous thrombosis and another report of superficial thrombophlebitis (blood clot in vein near the surface of the skin) but there were no cases of pulmonary embolism. As a risk of VTE has been identified with other COCs, the possibility of VTE events occurring during treatment with Lydisilka cannot be ruled out.
Risk factors and risk groups	Risk factors for VTE include: obesity (BMI >30 Kgm^2), prolonged immobilization, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma, positive family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50 years), increasing age (particularly above 35 years) and presence of other medical conditions associated with VTE (e.g. cancer, systemic lupus erythematosus, hemolytic uremic syndrome, chronic

	inflammatory bowel disease [Crohn's disease or ulcerative colitis)] and sickle cell disease).
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.1, 4.3, 4.4,4.6, 4.8* *PL section 2, 4* Additional risk minimization measures: *Educational materials:* **Important information for women:** *Information card for women* **Physician educational material:** *Checklist for prescribers*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: Arterial thromboembolism (ATE)	
Evidence for linking the risk to the medicine	The small increased risk of ATE (blood clots in the arteries) in women taking COCs has been known for many years and is very low. In the completed clinical studies, no ATE events were observed. However, as a risk of blood clots in the arteries has been identified with other COCs, the possibility of ATE events occurring during treatment with Lydisilka cannot be ruled out. Along with other factors, ATE can potentially cause a cerebrovascular accident (stroke) or a myocardial infarction (heart attack). In the clinical studies, no strokes and no heart attacks were observed.
Risk factors and risk groups	Risk factors for arterial ATE include: increasing age (particularly above 35 years), smoking, hypertension, obesity (BMI >30 Kgm^2), positive family history (ATE ever in a sibling or parent especially at relatively early age e.g. below 50 years), migraines and other medical conditions associated with adverse vascular events (e.g. diabetes mellitus, hyperhomocysteinemia, valvular heart disease and atrial fibrillation, dyslipoproteinemia and systemic lupus erythematosus).
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.3, 4.4, 4.8* *PL section 2, 4* Additional risk minimization measures: *Educational materials:* **Important information for women:** *Information card for women* **Physician educational material:**

	Checklist for prescribers
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Exposure during pregnancy	
Risk minimization measures	Routine risk minimization measures: *SmPC section 4.6, 5.3* *PL section 2* Additional risk minimization measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of Lydisilka.

II.C.2 Other studies in post-authorization development plan

Study short name and title:

International Active Surveillance Study: Evaluation of the safety of a combined oral contraceptive containing estetrol and drospirenone

Purpose of the study:

The primary objective is to characterize and compare the risks of Lydisilka with levonorgestrel-containing combined oral contraceptives in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is VTE, specifically DVT and PE. Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of ATE, describing the drug utilization pattern, describing the baseline risk for VTE and ATE and investigating outcomes associated with fetal exposure to Lydisilka.