Summary of the Risk Management Plan for Jaydess®

Active substance: Levonorgestrel 13.5 mg intrauterine delivery system

Version number: version 1.0

Document date: 31-Mar-2023

Based on the EU-RMP v8.3 for Jaydess®/Kyleena® (dated 21 OCT 2022)

Summary of the risk management plan

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Jaydess® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Jaydess® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Jaydess®.

The Summary of the Risk Management Plan for Jaydess® v1.0 is based on the Summary of Activities in the Risk Management Plan by Product for Jaydess® (levonorgestrel 13.5 mg intrauterine delivery system)/Kyleena® (levonorgestrel 19.5 mg intrauterine delivery system) of the EU-RMP v.8.3, dated 21 OCT 2022. Deviations in the risk minimization measures applicable for Switzerland from the EU-RMP are possible.

1. Summary of Risk Management Plan for Jaydess®

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

Jaydess' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jaydess should be used.

2. The Medicine and what it is used for

Jaydess is used for contraception for up to three years.

Jaydess is a levonorgestrel (LNG, active substance) releasing intrauterine delivery system (Levonorgestrel-Releasing Intrauterine System [LNG-IUS], total LNG content 13.5 mg). Jaydess is placed in the uterus with a preloaded, ready-to-use inserter.

Jaydess and Kyleena (Intrauterine System with LNG content 19.5 mg) have similar inserter and T-body dimensions and are referred to as "LCS" in this document when data relate to both products (LCS = low-dose levonorgestrel contraceptive intrauterine system; LCS12 = Jaydess and LCS16 = Kyleena).

3. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

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

Measures to minimise 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 authorised 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 minimise its risks.

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

In the case of Jaydess, these measures are supplemented *with additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

3.1 List of Important Risks and Missing Information

Important risks of Jaydess are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely used. 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 Jaydess. 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).

3.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	- Pelvic inflammatory disease - Ectopic pregnancy in case of contraceptive failure - Uterine perforation - Unintended pregnancy with LCS12/Jaydess
Important potential risks	- Potential for medication error - Potential for off-label use in indications other than contraception - Potential of use beyond approved duration of use
Missing information	- None

3.2 Summary of Important Risks

Important identified risk: Pelvic inflammatory disease (PID)	
Evidence for linking the risk to the medicine	As with other IUCs there is an increased risk of PID at the time of placement and during the first weeks after the placement (clinical trial evidence, epidemiological data).
Risk factors and risk groups	The risk of PID is increased in women with sexually transmitted infections, women who have multiple sexual partners and women who have had PID in the past.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.2, 4.3, 4.4, 4.8 Patient Information Leaflet (PIL): Section 2, 4 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	EURAS-LCS12 See Section 4 of this summary for an overview of the post - authorisation development plan.

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Important identified risk: Ectopic pregnancy in case of contraceptive failure	
Evidence for linking the risk to the medicine	Jaydess is very effective in preventing pregnancy. The absolute risk of ectopic pregnancy in LCS (LCS12/Jaydess and LCS16/Kyleena) users is low. However, when pregnancy occurs with LCS *in situ*, the pregnancy is more likely to be ectopic than in women who become pregnant without LCS in place. This is a risk which is common to all IUCs when contraceptive failure occurs (clinical trial evidence, observational study evidence). About half of the unintended pregnancies with LCS are ectopic pregnancies.
Risk factors and risk groups	The observed frequencies of ectopic pregnancy for LCS in subgroup analyses including age, parity and Body Mass Index (BMI) gave no evidence for a higher incidence in any of the subgroups studied. Some of the subgroups were too small for a conclusive assessment. *Risk factors for ectopic pregnancy in general:* Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. Age, smoking, prior abortions, prior PID, prior history of tubal surgery or infertility are associated with a higher risk. In adolescents, prior PID and gonorrhoea/*Chlamydia trachomatis* infection are the more important risk factors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4, 4.6, 4.8 PIL: Section 2 **Additional risk minimisation measures:** Education material
Additional pharmacovigilance activities	EURAS-LCS12 See Section 4 of this summary for an overview of the post-authorisation development plan.

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Important identified risk: Uterine perforation	
Evidence for linking the risk to the medicine	Uterine perforation may occur with the use of all types of IUC, including LNG-IUS (clinical trial evidence, observational study evidence).
Risk factors and risk groups	The risk of uterine perforation is increased in women who are breastfeeding at time of insertion or have given birth up to 36 weeks before insertion. The risk of perforation may be increased in women with fixed retroverted uterus.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.2, 4.3, 4.4, 4.8 PIL: Section 2, 4 **Additional risk minimisation measures:** None

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Important identified risk: Unintended pregnancy with Jaydess *in situ*	
Evidence for linking the risk to the medicine	Jaydess is very effective in preventing pregnancy. When intrauterine pregnancy occurs, the risk of spontaneous abortion and premature labour is increased. This is a risk which is common to all pregnancies occurring with intrauterine contraceptives (clinical trial evidence, observational study evidence and spontaneous post-marketing reporting). Evidence for risk of virilisation is based on information from isolated case reports. There have been isolated cases of masculinisation of the external genitalia of the female foetus following local exposure to LNG during pregnancy with an LNG-IUS in place.
Risk factors and risk groups	In the clinical trials with LCS, no differences were noted for subgroup analyses by age, parity and BMI. For some of the subgroup analyses the size of the subgroups was too small to allow for detection of differences in PI (Pearl Index). Incorrect position of the IUS (or partial or complete expulsion, uterine perforation) may decrease the effectiveness of LCS. *Risk factors for spontaneous abortion in general*: The risk of spontaneous abortion increases with maternal age and varies with obstetric history, e.g. women whose only or last pregnancy ended in early pregnancy loss are at increased risk of miscarriage. Women with uterine abnormalities including congenital anomalies or e.g. uterine leiomyoma, autoimmune and endocrine disorders, thrombophilia are at increased risk for early pregnancy loss. *Risk factors for preterm delivery in general:* Risk factors for preterm delivery include e.g. previous preterm delivery, first-trimester bleeding, low education, previous medical condition and new medical condition or health problem during pregnancy.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4, 4.6 PIL: Section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	EURAS-LCS12 See Section 4 of this summary for an overview of the post-authorisation development plan.

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Important potential risk: Potential for medication error	
Evidence for linking the risk to the medicine	Mirena and LCS16/Kyleena are approved for 5 years of use. LCS12/Jaydess is approved for 3 years of use. Each brand of LNG-IUS can be identified by its specific features. An incorrect decision on treatment continuation or IUS removal/replacement could theoretically occur in situations where the type of LNG-IUS that was inserted some years ago is not (no longer) known to the user or health care provider.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 3, 4.1, 4.2 **Additional risk minimisation measures:** Educational material and patient reminder card

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Important potential risk: Potential for off-label use in indications other than contraception	
Evidence for linking the risk to the medicine	LCS12/Jaydess or LCS16/Kyleena have not been studied in indications other than contraception. Off-label use of LCS12/Jaydess and LCS16/Kyleena in other indications Mirena is approved for (e.g., idiopathic menorrhagia, protection from endometrial hyperplasia during oestrogen replacement therapy) might occur but is expected to be low, since an effective treatment in the form of Mirena is available.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Clearly mentions approved indication in section 4.1 PIL: Clearly mentions approved indication in section 1 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	EURAS-LCS12 Drug Utilisation Study (DUS) for Jaydess See Section 4 of this summary for an overview of the post-authorisation development plan.

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Important potential risk: Potential of use beyond approved duration of use	
Evidence for linking the risk to the medicine	The efficacy of LCS12/Jaydess has been demonstrated for a full period of 3 years. Mirena and LCS16/Kyleena are approved for 5 years. Intentional use of LCS12/Jaydess for longer than the approved duration of use might occur, but the risk is estimated as low, given that the duration of use is clearly stated in the Product Label.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Clearly mentions duration of use in section 4.1 PIL: Clearly mentions duration of use in section 1 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	EURAS-LCS12 DUS for Jaydess See Section 4 of this summary for an overview of the post-authorisation development plan.

4. Post-authorisation Development Plan

4.1 Studies which are conditions of the Marketing Authorization

The following studies are conditions of the marketing authorisation:

EURAS-LCS12

European Active Surveillance Study of LCS12

Purpose of the study:

The EURAS-LCS12 study is designed to investigate whether Jaydess (LCS12) is associated with an increased risk of unintended pregnancy (including ectopic pregnancy) compared to Mirena and to copper IUDs. The objective is to assess among new users the risks of certain events (e.g., contraceptive failure rate, ectopic pregnancy and PID) associated with the use of LCS12/Jaydess compared with the established hormonal IUD Mirena and compared with established copper IUDs during standard clinical practice. In addition, drug utilisation patterns will be described.

4.2 Other Studies in Post-authorization Development Plan

DUS for Jaydess

Pharmacoepidemiological study (Drug Utilisation Study) of Jaydess use in routine clinical practice in Sweden.

Purpose of the study:

Jaydess is approved for contraception for a maximum of 3 years. The purpose of the study is to characterise new users of LCS12/Jaydess, to estimate the duration of LCS12/Jaydess method use, to study switching patters among women using LCS12/Jaydess and comparator method(s) as well as to study possible off-label use of LCS12/Jaydess.