

JAYDESS®/KYLEENA®
(levonorgestrel 13.5 mg/19.5 mg intrauterine delivery system)
EU Risk Management Plan

Part VI – Summary of the Risk Management Plan by Product

Summary of risk management plan for Kyleena

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

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

I. The medicine and what it is used for

Kyleena is used for contraception for up to five years.

Kyleena is a levonorgestrel (LNG, active substance) releasing intrauterine delivery systems (LNG-IUS, total LNG content 19.5 mg). Kyleena is placed in the uterus with a preloaded, ready-to-use inserter.

Kyleena and Jaydess (IUS with LNG content 13.5mg) 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).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kyleena, together with measures to minimise such risks and the proposed studies for learning more about Kyleena's 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 Kyleena, 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 analysed, including PBRER/PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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II.A. List of important risks and missing information

Important risks of Kyleena 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 Kyleena. 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 for Kyleena

Important identified risks	Pelvic inflammatory disease Ectopic pregnancy Uterine perforation Unintended pregnancy with Kyleena in situ Expulsion
Important potential risks	Potential for medication error Potential for off-label use in indications other than contraception
Missing information	None identified

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II.B. Summary of important risks

Important identified risk: Pelvic inflammatory disease

Evidence for linking the risk to the medicine	As with other intrauterine contraceptives there is an increased risk of pelvic inflammatory disease (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	<p>Routine risk minimization measures: <u>SmPC</u>: Section 4.2, 4.3, 4.4, 4.8 <u>PIL</u>: Section 2, 4</p> <p>Additional risk minimisation measures: None</p>

Important identified risk: Ectopic pregnancy

Evidence for linking the risk to the medicine	Kyleena 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 intrauterine contraceptives 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	<p>The observed frequencies of ectopic pregnancy for LCS in subgroup analyses including age, parity and 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.</p> <p><i>Risk factors for ectopic pregnancy in general:</i> 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</p>
Risk minimisation measures	<p>Routine risk minimization measures: <u>SmPC</u>: Section 4.4, 4.6, 4.8 <u>PIL</u>: Section 2</p> <p>Additional risk minimisation measures: Educational material</p>

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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 intrauterine contraceptives, 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 minimization measures: <u>SmPC</u> : Section 4.2, 4.3, 4.4, 4.8 <u>PIL</u> : Section 2, 4 Additional risk minimisation measures: None

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Important identified risk: Unintended pregnancy with Kyleena in situ

Evidence for linking the risk to the medicine	<p>Kyleena is very effective in preventing pregnancy. The nature of the risk is related to the presence of an intrauterine foreign body (risk of spontaneous abortion, premature labor). 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).</p>
Risk factors and risk groups	<p>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).</p> <p>Incorrect position of the IUS (or partial or complete expulsion, uterine perforation) may decrease the effectiveness of LCS.</p> <p><i>Risk factors for spontaneous abortion in general:</i> 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.</p> <p><i>Risk factors for preterm delivery in general:</i> 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.</p>
Risk minimisation measures	<p>Routine risk minimization measures:</p> <p><u>SmPC:</u> Section 4.4, 4.6</p> <p><u>PIL:</u> Section 2</p> <p>Additional risk minimisation measures:</p> <p>None</p>

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Important identified risk: Expulsion

Evidence for linking the risk to the medicine	Expulsion may occur with the use of all types of intrauterine contraceptives (IUCs), including Kyleena (clinical trial evidence, known for class).
Risk factors and risk groups	The expulsion rate was low regardless of age or parity. Generally, more partial and total expulsions occurred in parous than in nulliparous women. <i>IUD expulsion in general:</i> The risk of expulsion is somewhat increased when an IUD is inserted immediately post partum (“post-placental”), and significantly increased >48 hours to 4 weeks after delivery.
Risk minimisation measures	Routine risk minimization measures: <u>SmPC:</u> Section 4.2, 4.4, 4.8 <u>PIL:</u> Section 2, 4 Additional risk minimisation measures: None

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 minimization measures: <u>SmPC:</u> 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 estrogen 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 minimization measures: <u>SmPC</u> : Clearly mentions approved indication Additional risk minimisation measures: None

II.C. Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Kyleena. The results of the studies conducted with LCS12/Jaydess will be applicable for LCS16/Kyleena.

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

There are no studies required for Kyleena by EMA (European Medical Agency) or any other national competent authority in the EU.