MIRENA®
(levonorgestrel 52 mg intrauterine delivery system)
EU Risk Management Plan

Summary of the Risk Management Plan for Mirena

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Active substance(s) (INN or common name):	Levonorgestrel

Medicinal products to which this RMP refers:	Mirena

Name of Marketing Authorisation Holder or Applicant:	Bayer (affiliates)

Data lock point for this module	08 MAY 2019

Version number of RMP when this module was last updated	1.1

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

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

I. The medicine and what it is used for

Mirena is approved and marketed in all EU countries and in the EEA countries Norway and Iceland.

The Mirena indications contraception and idiopathic menorrhagia/heavy menstrual bleeding are approved in all the countries. Protection from endometrial hyperplasia during estrogen replacement therapy is an approved indication in most of the countries (not approved in Germany, France, Poland, Portugal and Spain). Additionally, the indication dysmenorrhea is approved in Finland.

Mirena is a levonorgestrel (LNG, active substance) intrauterine delivery system (LNG-IUS, total LNG content 52 mg). Mirena is placed in the uterus with a preloaded, ready-to-use inserter.

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

Important risks of Mirena, together with measures to minimise such risks and the proposed studies for learning more about Mirena'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 Mirena, 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 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 Mirena 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 Mirena. 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	Uterine perforation Pelvic inflammatory disease Risk associated to intrauterine pregnancy with Mirena in situ Ectopic pregnancy in case of contraceptive failure Expulsion
Important potential risks	Potential for medication error
Missing information	None identified

II.B Summary of important risks

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:** SmPC Section 4.2, 4.3, 4.4, 4.8 PIL Section 2, 4 Insertion instruction **Additional risk minimisation measures:** None

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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	**Routine risk minimization measures:** SmPC: Section 4.2, 4.3, 4.4, 4.8 PIL: Section 2, 4 Insertion instruction **Additional risk minimisation measures:** None

Important identified risk: Risk associated to intrauterine pregnancy with Mirena in situ	
Evidence for linking the risk to the medicine	Mirena 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).
Risk factors and risk groups	*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 minimization measures:** SmPC: Section 4.3, 4.4, 4.6 PIL: Section 2, 3, 4 **Additional risk minimisation measures:** None

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Important identified risk: Ectopic pregnancy in case of contraceptive failure	
Evidence for linking the risk to the medicine	Mirena is very effective in preventing pregnancy. The absolute risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in situ, the pregnancy is more likely to be ectopic than in women who become pregnant without Mirena 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 Mirena are ectopic pregnancies.
Risk factors and risk groups	*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. *Risk factors for ectopic pregnancy in the adolescent population*: In the absence of prior history of ectopic pregnancy and prior tubal surgery in the adolescent population, prior PID and prior gonorrhoea/ chlamydia trachomatis infection are the more important risk factors in this population. Ectopic pregnancy in adolescents is more often associated with current gonorrhoea/ chlamydia trachomatis infection.
Risk minimisation measures	**Routine risk minimization measures:** SmPC: Section 4.4, 4.6, 4.8 PIL: Section 2, 4 **Additional risk minimisation measures:** Educational material

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 Mirena (clinical trial evidence, known for class).
Risk factors and risk groups	The risk of expulsion is somewhat increased when an IUC is inserted immediately post-partum (“post-placental”), and significantly increased when inserted >48 hours to 4 weeks after delivery. A risk for expulsion may be increased due to anatomical factors. A tendency for higher expulsion rates in the indication idiopathic menorrhagia compared to the use in the indication contraception has been observed for Mirena. Published literature indicates an increased risk of expulsion in women with dysmenorrhea associated with adenomyosis.
Risk minimisation measures	**Routine risk minimization measures:** SmPC: Section 4.2, 4.4, 4.8 PIL: Section 2, 3, 4 **Additional risk minimisation measures:** None

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Important potential risk: Potential of medication error	
Evidence for linking the risk to the medicine	Three LNG-IUSs are marketed by Bayer (Mirena, Jaydess, Kyleena). Mirena and Kyleena are approved for 5 years of use. 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:** SmPC: Section 3, 4.1, 4.2 **Additional risk minimisation measures:** Educational material and patient reminder card

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 Mirena (within the EU).

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

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