Part VI: Summary of the risk management plan

Summary of risk management plan for Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System (levonorgestrel)

This is a summary of the risk management plan (RMP) for Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System. The RMP details important risks of Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System, how these risks can be minimised, and how more information will be obtained about Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System's risks and uncertainties (missing information).
Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System should be used.

I. The medicine and what it is used for

Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System is authorised for contraception and treatment of heavy menstrual bleeding (see SmPC for the full indication). It contains levonorgestrel as the active substance and it is inserted into the uterine cavity within seven days of the onset of menstruation.

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

Important risks of Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System, together with measures to minimise such risks and the proposed studies for learning more about Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System'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 Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System, 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 PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System. 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);

Summary of safety concerns	
Important identified risks	#1. Uterine perforation
	#2. Ectopic pregnancy
	#3. Expulsion of device
Important potential risks	#4. Off label use/ (use in other indication, prolonged use)
	#5. Medication error (product confusion)
Missing information	none

II.B Summary of important risks

Uterine perforation*	
Evidence for linking the risk to the medicine	This safety concern was identified during the development and post-marketing period.
Risk factors and risk groups	Risk factors associated with increased risk of perforation at time of IUD insertion include clinician inexperience, stenotic cervix, and immobile or retroverted uterus. The type of IUD does not appear to impact perforation risk.[4] A large prospective comparative non-interventional cohort study with other IUS and IUD showed that both breastfeeding at the time of insertion and insertion up to 36 weeks postpartum were associated with an increased risk of perforation. These risk factors were independent of the type of IUS/IUD inserted.[4]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8 PL section 3, 4 and Instructions for use and handling Prescription status: Prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures are proposed

Ectopic pregnancy	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with levonorgestrel intrauterine device.
Risk factors and risk groups	Ectopic pregnancies are more prominent among intra-uterine devices containing levonorgestrel due to the fact that ovulation is often not suppressed in LNG-IUD users and based on the predominantly local contraceptive effect, LNG-IUD may prevent intrauterine pregnancy more efficiently than ectopic pregnancy. Ectopic pregnancies can be associated with reduced fertility especially if the pregnancy is recognized late. Furthermore, LNG-IUDs may prevent the patient's menstruation so that the risk not to recognize a pregnancy is even higher for these long-acting contraceptive methods.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, 4.6 and 4.8 PL section 2 and 4 Prescription status: Prescription only medicine Additional risk minimisation measures: Combined healthcare professional brochure

Expulsion of device	
Evidence for linking the risk to the medicine	This safety concern was identified during the clinical study (M360-L102) with levonorgestrel intrauterine device and from literature.
Risk factors and risk groups	A small increased risk of expulsion of an IUC can be observed after abortion (early insertion 9.7% delayed insertion 7.4%).[15]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 3 and 4 Prescription status: Prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures are proposed

Off label use (use in other indication, prolonged use)	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with levonorgestrel intrauterine device.

[15] FSRH Guideline. Intrauterine Contraception (Updated October 2015)

Risk factors and risk groups	Patients that need the product for other indications than contraception and heavy menstrual bleeding
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1, 4.2 and 5.1 PL section 1 and Instructions for use and handling Prescription status: Prescription only medicine Additional risk minimisation measures: Patient reminder card, Combined healthcare professional brochure, Prescriber Checklist

Medication error (product confusion)	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with levonorgestrel intrauterine device.
Risk factors and risk groups	Patients that need the product for other indications than contraception and heavy menstrual bleeding
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 PL section Instructions for use and handling Prescription status: Prescription only medicine Additional risk minimisation measures: Combined healthcare professional brochure, Prescriber Checklist

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 Levonorgestrel (20 micrograms/24 hours) Intrauterine Delivery System

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

There are no studies required for Levonorgestrel 20 microg/ 24 h Intrauterine Delivery System