Part VI: Summary of the risk management plan

Summary of risk management plan for Levosert / Levosert One / Levosert Two / Levonorgestrel "Richter" and Donasert (levonorgestrel)

This is a summary of the risk management plan (RMP) for Levosert / Levosert One / Levosert Two / Levonorgestrel "Richter" and Donasert, hereinafter referred to as Levosert. The RMP details important risks of Levosert, how these risks can be minimised, and how more information will be obtained about Levosert's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Levosert 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 administered by insertion into the uterine cavity.

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

Important risks of Levosert, together with measures to minimise such risks and the proposed studies for learning more about Levosert'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 Levosert, 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 Levosert 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 Levosert. 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	Uterine perforation
	Ectopic pregnancy
Important potential risks	Off-label use (use in other indication, prolonged use)
	Medication error (product confusion)
Missing information	None

II.B Summary of important risks

Important identified risk: Uterine perforation	
Evidence for linking the risk to the medicine	This risk 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. 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. (Heinemann K, Reed S, Moehner S, Minh TD. Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. Contraception. 2015; 91(4): 274-9)
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4 and 4.8* *PL sections 3, 4 and Instructions for use and handling* *Legal status: prescription only medicine* Additional risk minimisation measures: No additional risk minimisation measures

Important identified risk: Ectopic pregnancy	
Evidence for linking the risk to the medicine	This risk was identified in the phase 3, multi-centre, open-label study (M360-L102) of a levonorgestrel-releasing intrauterine system for long-term, reversible contraception; and from the literature
Risk factors and risk groups	Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry an increased risk of ectopic pregnancy.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.6 and 4.8* *PL sections 2 and 4* *Legal status: prescription only medicine*

	Additional risk minimisation measures: *Combined healthcare professional brochure*

Important potential risk: Off-label use (use in other indication, prolonged use)	
Evidence for linking the risk to the medicine	This risk 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 sections 4.1, 4.2 and 5.1* *PL section 1 and Instructions for use and handling* *Legal status: prescription only medicine* Additional risk minimisation measures: *Patient reminder card* *Combined healthcare professional brochure* *Prescriber checklist*

Important potential risk: Medication error (product confusion)	
Evidence for linking the risk to the medicine	This risk is plausible due to having two inserters on the market.
Risk factors and risk groups	Physicians familiar with only one insertion technique. 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* *Legal 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 Levosert.

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

There are no studies required for Levosert.