Final Lead Member State
PSUR Follow-Up assessment report

Active substance(s): levonorgestrel

Procedure No.: DE/H/PSUFU/00001856/201712 (Part I)

Procedure resources	
Lead Member State (LMS)	DE

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1. Background information on the procedure

This is the assessment of Follow-Up information for levonorgestrel as agreed with the PSUSA assessment PSUSA/00001856/201712.

CMDh adopted the following question to the MAH(s):

"In view of potential misinterpretation of the risks associated with products due to different communication approaches, MAHs are requested to evaluate the effectiveness and necessity of the current educational material for the LNG-containing IUDs and provide an analysis of which safety concerns and key elements should be addressed by the educational material. This should be provided via the same PSUSA-follow-up procedure as above (DE/H/PSUFU/00001856/201712) to be submitted to the LMS (DE) within 3 months after the finalisation of the PSUSA-procedure."

CMDh agreed that the response(s) are submitted and assessed within an informal work-sharing procedure for follow-up for PSUSA for NAPs and appointed [MS] as Lead Member State.

2. Final assessment conclusions and actions

The current PSUSA-follow-up procedure covers intrauterine devices (IUDs) containing the second generation progestin levonorgestrel (LNG). In cases of IUDs, the contraceptive effect of levonorgestrel is mainly locally by inhibiting the growth of the uterine lining and causing a change in the mucus of the cervix so that it gets viscous and impervious to sperm. Authorized indications are hormonal contraception and hypermenorrhoea. In several European countries, it is also authorized for idiopathic menorrhagia and for protection from endometrial hyperplasia during estrogen replacement therapy. The European Union reference date for the first LNG-IUD was 09.05.1990. Since 1990, further LNG-containing IUDs with the same (52 mg LNG) or lower LNG-dosages have been authorized (i.e. Jaydess: 13.5 mg, Kyleena: 19.5 mg).

For LNG-containing IUDs different educational material is in place highlighting one or more safety concerns and to remind/advice HCPs and patients how to avoid risks and handle the different IUDs. However, an internal survey performed by one MAH suggested that the different communication approaches addressing the risk of ectopic pregnancy may result in misinterpretation of the risks associated with the products.

The concerned MAHs provided information on the additional risk minimisation activities (aRMM) implemented for their LNG-IUDs and one MAH commented that no aRMM is in place.

Additional RMMs to reduce the risk of ectopic pregnancy exists for Jaydess (part of the RMP) and at national level for Mirena. In the current SmPCs for LNG-IUDs the risks of ectopic pregnancies are in the same magnitude and the numbers are too low to base any statistics upon that would describe differences. The EURAS-LCS12 study is currently generating real-world use data on comparative contraceptive failure rates, including ectopic pregnancy rates, for Jaydess, Mirena and copper IUDs. The final study report will be available in Q4/2022. Since the risk of ectopic pregnancy is more prominent for LNG-IUDs compared to other contraceptive methods because ovulation is not always suppressed by LNG-IUDs and intrauterine pregnancy is supressed more effectively than ectopic pregnancy, this aRMM is of relevance and helpful for all HCPs to inform their patients receiving LNG-IUDs.

Furthermore, aRMM is in place to avoid any medication error that might be associated with the different durations of use and different indications approved. Although no AEs mentioning a mix-up of different LNG-IUDs have been identified and although according to the MAH, the content of the brochure that helps distinguishing between the MAH's LNG-IUDs is sufficiently known by physicians,

this aRMM is still considered helpful for the HCPs and may avoid an inadvertent mix-up in future. Therefore, a single brochure addressing the risk of ectopic pregnancy and the risk of medication error with distinguishing features should be implemented for all LNG-IUDs.

In addition, a patient reminder card, currently part of the RMP for Kyleena and Jaydess to reduce the potential risk of medication error due to the different durations of use and different indications approved for the LNG-IUDs, should be implemented for all LNG-IUDs. This card reminds patients on the day of insertion, the IUD (and active substance) implemented, the latest day of removal and links to the latest product information leaflet. A waiver may be agreed with the respective national competent authority in cases with other measures in place to convey this information to the patient.

The aforementioned aRMM should be embedded in a (updated) risk management plan (RMP) to be submitted within six months after the finalisation of the PSUSA-follow-up procedure. At national level further aRMMs are in place highlighting one or more of the safety concerns mentioned above. The need for such further educational material is at the distinction of NCAs.

Scientific conclusions and grounds for a recommendation to update the RMP

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. The risk of ectopic pregnancy is already labelled in the product information of each levonorgestrel-containing intrauterine device with comparable magnitudes. Therefore, it is reasonable to implement similar communication approaches for all LNG-IUDs until numbers are sufficient to base comparative statistics upon. To avoid ectopic pregnancies by highlighting the risk factors more detailed than in the SmPC/PIL and by advising the prescriber to inform the patients about the symptoms associated with an ectopic pregnancy, an ectopic pregnancy brochure for prescribers should be implemented for all LNG-IUDs.

Concerning the risk of medication errors different educational material exists: The patient reminder card forms part of the EU product labeling for Jaydess and Kyleena and is supplied with every package. It is listed as aRMM in the current RMP for Kyleena/Jaydess to reduce the important potential risk of medication error. The LNG-IUDs available on the market have different approved durations and different approved indications. Therefore, this patient reminder card is of relevance for all LNG-IUDs and should be implemented as aRMM accordingly in order to remind the patient on the IUDs-brand name (and active substance) that has been inserted, the indication, the day of insertion, the latest day of removal and the next check-ups. Furthermore, it helps identifying the LOT number and refers to the products latest product information.

Since no case reports have been identified describing a mix-up of different LNG-IUDs and due to the information that HCPs use the already implemented brochure with distinguishing features, this brochure may help HCPs to distinguish between the LNG-IUDs and avoid any mix-ups. A combined HCP-brochure addressing the risk of ectopic pregnancy and the risk of medication error should be implemented for all LNG-IUDs. The following key elements are considered relevant for distinguishing between the LNG-IUDs: distinctive characteristics of the products (e.g. size, colour of threads) including pictures (detailing whether there is a silver ring or not) as well as different indications and durations of use of the products and how to recognize them via ultrasound (2D and 3D imaging) and X-ray.

Additional RMMs, as evaluated above, should be embedded in a risk management plan. Therefore, MAHs are requested to submit a (updated) risk management plan within 6 months after the finalization of this PSUSA-follow-up procedure.

3. Final Recommendations

RMP

Based on the review of data submitted, the LMS considers that the RMP should be updated as follows:

1. Address the risk of ectopic pregnancy and the risk of medication error with aRMMs i.e. a combined healthcare professional brochure including the following key elements:

a) The risk of ectopic pregnancy in case of contraceptive failure

b) Information concerning the background incidence for ectopic pregnancies

c) Signs and symptoms of ectopic pregnancy

d) Influence on the patient's fertility

e) Risk factors for ectopic pregnancies

f) Advice to hand over the product information leaflet to the patient before insertion of the IUD

g) The need to thoroughly counsel a woman regarding the risk, signs and symptoms and monitoring of ectopic pregnancy

h) Distinctive characteristics of the products (e.g. size, colour of threads) including pictures (detailing whether there is a silver ring or not)

i) Different indications and durations of use of the products and

j) How to recognize them via ultrasound (2D and 3D imaging) and X-ray.

2. Address the risk of medication error with aRMMs i.e. a patient reminder card with the following key elements (a waiver may be agreed with the respective national competent authority in cases with other measures in place to convey this information to the patient):

a) IUDs-brand name (and active substance)

b) indication

c) day of insertion

d) latest day of removal

e) LOT number

f) HCP contact details

g) Link to the latest product information leaflet (local NCA-Homepage)

3. The aforementioned aRMMs should be embedded in a risk management plan (RMP). MAH's should submit a (updated) risk management plan in line with the underlying Guideline on good pharmacovigilance practices Module V (rev. 2) within 6 months following the finalization of this PSUFU.

4. Issues to be addressed in the next PSUR

None

5. PSUR frequency

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.