Active Post Marketing Surveillance (APMS)

Medicinal product:	Levonorgestrel 20 micrograms/24 hours Intrauterine System (IUS) (Levosert® and other associated brand names)
Indication(s):	Heavy Menstrual Bleeding/ Contraception (*)
Protocol number :	010-100
Version number:	Amendment 02
Date:	18th June 2014
Title of the study:	Active post-marketing surveillance of Levonorgestrel IUS insertion related difficulties: a non-interventional post-authorisation safety study

Document Approval:

Heather Thomas, Executive Director, Clinical Research
Date:

Jean-Michel Foidart, Chief Scientific Officer
Date:

Christina Guiton, Deputy European QPPV
Date:

(*) *As applicable*

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1. Rationale and Background

Levonorgestrel IUS (Levosert® and other associated brand names) a hybrid (art. 10(3) Dir 2001/83/EC) generic of Mirena® (Mirena) (1), is a levonorgestrel (LNG) intrauterine delivery system (IUS) indicated for heavy menstrual bleeding and contraception (N.B.: *As applicable).*

In complement to safety information collected in the Phase 3 clinical trials LVS-20 and M360-L102, and as part of the Risk Management Plan (RMP), the post-authorisation safety study (PASS) will be initiated during the early post-marketing phase of Levonorgestrel IUS to assess the risks linked to insertion-related difficulties in a study population that is representative for the actual users of the Levonorgestrel IUS and thus confirm the safety profile of this IUS under normal conditions of use.

2. Research question and objectives

The primary objective of this PASS is to characterize, under routine practice, the ease of insertion and the safety profile of Levonorgestrel IUS during insertion in a study population that is representative of the actual users of the IUS (either new user and patients switching from Mirena).

The secondary objective of the study is to characterize the utilization pattern for Levonorgestrel IUS.

3. Study design

This study is a non-interventional, open label, multi centre, uncontrolled, post approval safety study of levonorgestrel IUS in the United Kingdom, and all EU/EEA countries where the Levonorgestrel IUS has received a Marketing Authorization, using stimulated reporting to assemble safety data of special interest from a large number of patients.

4. Population

The 'exposure' data for this study come from women in whom Levonorgestrel IUS is inserted for any indication, including the licensed indication, and for whom a Health Care Professional (HCP) has completed and submitted the form to the Sponsor/MAH.

Data collection will not interfere with the prescribing behavior of physicians or with the individual needs of the patient. Since this is an active surveillance study conducted in a naturalistic setting, open patient entry criteria are desirable to maximise external validity. There are no specific medical inclusion or exclusion criteria.

5. Variables

Main outcomes of interest are the following:

- Ease of insertion: assessed by a 2- point scale: easy/difficult
- Nature of insertion: if local anaesthesia, rigid dilation and/or ultrasound were used
- Related adverse events (unsolicited) occurring during placement or soon after placement, including but not limited to:

- Vasovagal events
- Pain related to placement
- Expulsion
- Uterine perforation
- Other adverse event considered relevant by the HCP

- Indication/s for use

6. Data sources

Data will be collected by stimulated reporting. During the early post-marketing phase, data collection forms (DCF) will be provided to the doctors. The way of distribution will be defined nationally. The DCF has been designed to be user-friendly and easy to complete.

7. Study size

The sample size has been estimated using SAS 9.2 (Proc Power) for difficulty levels of insertion to ensure that the 95% exact Clopper-Pearson confidence interval is included within the true incidence rate with a power of 80%.

A prospective post marketing study conducted on Mirena showed that the incidence of insertion-related difficulties with this IUS is close to 4% (2). It can be postulated that a similar incidence of insertion-related difficulties will be experienced with Levonorgestrel IUS. If the true incidence is 4%, a sample size of 918 patients ensures that the 95% exact confidence interval has a probability of at least 80% to be included within [2% to 6%].
In order to ensure enough eligible women with valid and complete information are included in the study, a sample size of 1000 women is desirable for this study. The sample size may be reassessed dependent on study progress over time.

8. Data analysis

DCF information will be entered in the Clinical and, partially, in the Pharmacovigilance databases. Progress reports will be produced and reviewed internally from study start in a frequency depending on the response rate of return of questionnaires (i.e.: at approximately 100, 250, 500 and 1000 received questionnaires). An annual safety report will be provided to Reference Member State (UK) and will be available at the request of other relevant regulatory agencies.

The progress report will include a qualitative assessment of the summary characteristics of patients reported with these outcomes: evaluation of treatment details, the detection and clinical features and management of device insertion problems, summary of treatment-related adverse events , the patient's relevant medical and medication history. Details of treatment initiation and prescribing reasons as reported on the questionnaire will be provided using descriptive statistics. Prescribing pattern will be assessed.

The reported insertion problems will be provided in a listing which will also be part of the Final Clinical Study Report. Further details on analysis and reporting will be included in a separate statistical analytical plan (SAP). The SAP will be generated to describe all summaries that will be provided.

General comments about the readability of the instructions for use and handling will be recorded and summarised for future potential improvements of the instruction document.

9. Milestones

Start of data collection	At launch of product Expected by Q1 2015
End of data collection	Anticipated to continue until validated questionnaires have been returned for approximately 1,000 patients. However, duration of the study will be influenced by the level of prescribing of Levonorgestrel IUS by HCP and the rate of reporting Expected Q4 2015
Study progress report(s)	Depending on response rate after launch of study, approximately after 100, 250, 500 and 1000 received questionnaires Expected Q3 2015
Final report of study results	Maximum 12 months after study end (last questionnaire received) Expected Q1 2016

INTERNAL USE ONLY
For Pharmacovigilance use - Local Case Transmission Number: _____
For Clinical Data Management use - Data Management Number: _____

FORM ON EASE OF INSERTION

Guidance for completion:

We need your help in obtaining a description of the ease of insertion of <*Levonorgestrel IUS*> and insertion-related adverse events. The information is used to evaluate the safety of our product and to fulfill regulatory obligations. Please send the form as soon as you attempted or completed insertion of <*Levonorgestrel IUS*>.

- **Complete ALL fields to the best of your ability**
- **Please sign and date below**
- **Please note: the identity of the patient and all healthcare reporters will be kept confidential and will only be used to fulfill regulatory reporting obligations**
- **Please contact the local pharmacovigilance team in case of follow-up or additional adverse event(s)**

Report Type	☐ Initial report	
	☐ Follow-up report (to initial related adverse event)	Follow-up report Nr: _____

Patient Data:

Patient initials: ☐☐☐ (3 letters)

Year of birth: _____

Weight: Kg

Stone/Lbs _____

Height: Cm

Feet/Inch _____

Parity: _____

Gravida: _____

If Parity >1 :
Date of birth of last-born child

_____
(DD / MMM / YY)

Lactating: ☐ Yes ☐ No
If recently lactating, date of stopping

_____
(DD / MMM / YY)

Medication:

Medication (Trade name)	**Insertion/Attempt Date and time** (DD / MMM / YY; HH:MM)	**Indication(s)**	**Batch number**

Note: in case of device failure, please retain it, and contact the company representative to arrange its return and the completion of a complaint form.

Placement Visit

1. Date Last Menstrual Period Began: _____(DD / MMM / YY)
On Menses at Time of <*Levonorgestrel IUS*> Placement Attempt? ☐ Yes ☐ No

2. Was this the first attempt of insertion of any IUS for this patient? ☐Yes ☐No
If NO, please give the number of previous failed IUS insertions: _____
If NO, when did the last attempt occur? ☐ Less than or equal to 3 months ago
☐ More than 3 and up to 12 months
☐ More than 12 months ago
If NO, was the last attempt of insertion performed with < *Levonorgestrel IUS*>? ☐Yes ☐No
If NO, please provide trade name of IUS previously inserted:

_____

3. Was placement completed successfully this time? ☐Yes ☐No
If placement was **not successfully** completed, please explain:

_____

_____

If placement was **successfully** completed, please rate the ease/difficulty of placing <*Levonorgestrel IUS*>:
☐Easy
☐Difficult

4. Was local anesthesia used? ☐Yes ☐No
If **YES**: a) Cervical lip just for tenaculum placement? ☐Yes ☐No
b) Given during procedure for clinical necessity? ☐Yes ☐No
If **YES**: a) Due to discomfort during sounding? ☐Yes ☐No
b) Due to discomfort during IUS placement? ☐Yes ☐No
c) Other, specify: _____

5. Was rigid dilation performed? ☐Yes ☐No
If **YES**: ☐OS Finder
☐Pratt Dilator Largest Dilator Size Used: _____
☐Other, specify: _____

6. Was ultrasound guidance used? ☐Yes ☐No

7. Was placement performed per instructions? ☐Yes ☐No
If **NO**, please explain:

_____

_____

8. What is your general opinion about the readability of the "Instructions for use and handling"?
☐ Very Good ☐ Good ☐ Neutral ☐ Bad ☐ Very bad

9. During or after placement, did any adverse event(s) occur which you believe are RELATED to the IUS?

☐ Yes ☐ No

If **NO**, please go to question 10

If **YES**, please complete below:

Adverse Event Description	Onset date and time	Stop date and time	Is the related adverse event recovering?	Did AE abate after the IUS removal?	Did AE reappear after new IUS placement ?
Adverse event #1: _____ _____ _____			☐ Recovered/Resolved ☐ Not recovered/Not resolved ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown	☐ Yes ☐ No ☐ N/A (device not removed)	☐ Yes ☐ No ☐ N/A (device not replaced)
Adverse event #2: _____ _____ _____			☐ Recovered/Resolved ☐ Not recovered/Not resolved ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown	☐ Yes ☐ No ☐ N/A (device not removed)	☐ Yes ☐ No ☐ N/A (device not replaced)
Adverse event #3: _____ _____ _____			☐ Recovered/Resolved ☐ Not recovered/Not resolved ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown	☐ Yes ☐ No ☐ N/A (device not removed)	☐ Yes ☐ No ☐ N/A (device not replaced)
Adverse event #4: _____ _____ _____			☐ Recovered/Resolved ☐ Not recovered/Not resolved ☐ Recovered/Resolved with sequelae ☐ Fatal ☐ Unknown	☐ Yes ☐ No ☐ N/A (device not removed)	☐ Yes ☐ No ☐ N/A (device not replaced)

Seriousness Rating:
Did any of the adverse events above meet any of the definitions below to indicate it was a Serious AE?
☐ Yes ☐ No

If Yes, check the box that describes the reason for seriousness of the applicable AE:
☐ Patient died (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)
☐ involved or prolonged in patient hospitalization (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)
☐ involved persistent or significant disability or incapacity (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)
☐ life threatening (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)
☐ congenital anomaly/birth defect (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)
☐ Other medically important reason (☐ AE#1 ☐ AE#2 ☐ AE#3 ☐ AE#4)

Treatment of related adverse event:

Treatment /Procedure (if drug provide INN, generic or trade name)	**Dosing Regimen & Frequency of Dosing**	**Form / Route**	**Start Date** (DD / MMM / YY)	**End Date** (DD / MMM / YY) or N/A if continuing	**Indication (adverse event)**

Other concomitant medications (Please complete all drugs (including OTC) / vaccines taken by the patient within 3 months prior to or since the insertion/attempt)

Reported Drug/ Vaccine/ OTC Name (generic or trade name)	**Dosing Regimen & Frequency of Dosing**	**Form / Route**	**Start Date** (DD / MMM / YY)	**End Date** (DD / MMM / YY) or N/A if continuing	**Indication**

Other relevant tests and investigations:

Other relevant medical history:

Have you previously reported this related adverse event to a Regulatory Agency?

☐Yes Reg. Agency ref. nr: _____ ☐No

10. Any comments you want to share:

Reporter's name: _____ **Title:** _____

Clinic/Hospital Name: _____ **Occupation:** _____

City: _____ **Country:** _____

Telephone no: _____ **Fax no:** _____

Reporter's signature: _____ **Date:** _____

Please send this form immediately after placement to:
<To be completed nationally (fax + email+ postal address)>

To report further adverse events involving *<Levonorgestrel IUS>* after the visit where *<Levonorgestrel IUS>* was inserted, please contact our local pharmacovigilance team: *<to be completed nationally>*.

In addition to completing this form, you might also, depending on national requirements, need to report the event directly to your health authorities.

Thank you for your kind collaboration

10. References

1. Velev R. A multiple center, randomised, parallel group, single-blind clinical trial, to assess the therapeutic equivalence in terms of efficacy and safety of Test product (Levosert®) and Reference product (Mirena®) in patients with menorrhagia - Phase III (Therapeutic equivalence). 1-134. 17-6-2010.
2. Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, van Dam PA. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. Fertil Steril 2008; 90(1):17-22.