Jenapharm

Jenapharm GmbH & Co. KG • D-07740 Jena

[redacted]

[redacted]

Leverkusen, 28 September 2015

**Subject:**
**Intrauterine contraceptives - update on risk of uterine Perforation - class effect**
**Information on Direct Healthcare Professional Communication (DHPC) in Italy**

Products concerned:
Mirena (Reg. No.: 30495.00.00; 2130495);
Mirena Duplicate (Reg. No.: 41880.00.00; ENR: 2141880)
Jaydess (Reg. No.: 86537.00.00; ENR: 2186537)

Dear Madam/Sir,

In our objective to keep you continuously informed about worldwide regulatory actions regarding our products we wish to inform you herewith about the decision of the Italian health authority (AIFA) to request Bayer to distribute a "Direct Healthcare Professional Communication" (DHPC) to Healthcare Professionals (HCPs) in Italy for the intrauterine contraceptives (IUCs) Mirena and Jaydess. There is no parallel request for copper intrauterine devices (Cu IUDs).

The DHPC was distributed to Healthcare Professionals in Italy on 21st September 2015 as agreed with AIFA.

The DHPC informs HCPs in Italy about the updated information regarding uterine perforation associated with the use of intrauterine devices. The updated information is based on the finalized report of the "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD). The final data showed that there is a higher risk of uterine perforation in breastfeeding women and also in women who are up to 36 weeks post-partum at the time of insertion for both levonorgestrel-intrauterine system (LNG-IUS) and copper IUDs (Cu IUDs). The DHPC also informs about incidences of perforation for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women). In addition, the DHPC provides a summary of the EURAS-IUD.

Furthermore, the DHPC advises HCPs to take this information into consideration when selecting IUCs for use in patients who are less than 36 weeks post-partum or breastfeeding at the time of insertion. Healthcare professionals are also encouraged to inform patients on the risks of uterine perforation before the procedure. Patients should be educated on self-check for the removal threads of IUCs and possible signs of this complication.

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The DHPC is enclosed for your information.

**Background**

In **Italy**, Mirena is approved since January 1996 and the product was launched in October 1998. Approved indications for Mirena are contraception, idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy. Jaydess is approved since December 2013 and the product was launched in May 2014. Jaydess is approved for contraception.

In March 2015 an **European Union (EU)** wide labeling variation procedure for Mirena and Jaydess related to EURAS-IUD ended positively. An additional outcome of the procedure was that Member States could decide to ask for "Direct Healthcare Professional Communication" (DHPC) regarding risk of uterine perforation if considered appropriate in a particular Member State. There was no pan-EU communication decided upon. To date, some EU countries have contacted Bayer with respect to the potential for a DHPC. Bayer has responded to these requests with its position that the other communication tools that Bayer intends to use, in addition to the updated product labeling, are most appropriate to communicate the safety information deriving from the results of the EURAS-IUD study. The health authorities in the Czech Republic, Germany, Denmark, Italy, Portugal, Slovenia, Spain and the United Kingdom disagreed with Bayer's opinion and requested that a national DHPC be issued.

Outside of the EU, the health authorities in Egypt, Hong Kong, Serbia, Singapore and South Africa requested that a DHPC related to EURAS-IUD be issued.

**Company position**

EURAS-IUD is a large prospective, comparative, non-interventional cohort study in IUC users, including LNG-IUS (Mirena) and copper IUDs, with primary outcome of uterine perforation.

Uterine perforation is a complication associated with many gynaecological diagnostic, therapeutic and other procedures, including placement of IUCs. The risk of uterine perforation is not product-specific but can be considered a class effect of all IUCs currently marketed. The risk of uterine perforation, including risk factors such as breastfeeding and recent delivery, is explicitly described in the product information of all intrauterine devices. These product information have been continuously updated as new data on this risk have become available. Local SmPCs and PLs were updated accordingly.

Bayer is continuously monitoring the safety data of its intrauterine contraceptives. While providing further insight in the known risk of uterine perforation and its risk factors, the recently finalized study report of EURAS-IUD does not give rise to a new safety concern and reaffirms the positive benefit risk profile of intrauterine contraceptives. This is also the case for breast-feeding women and women who have recently delivered. Bayer considers that the final results of EURAS-IUD, while providing more detailed information on risk groups for uterine perforation, have neither changed the overall benefit-risk balance of their intrauterine contraceptives nor their condition of use.

Yours sincerely,

[redacted]

IMPORTANT INFORMATIVE NOTICE AGREED WITH EUROPEAN REGOLATHORY AUTHORITIES AND ITALIAN DRUG AGENCY (AIFA)

# Intrauterine contraceptives - Update on risk of uterine perforation

Dear Healthcare Professional,

In agreement with Bayer and AIFA, this letter is to update you on findings from the "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD). This was a large prospective, comparative, non-interventional cohort study of intrauterine contraception (IUC), in which were used copper intrauterine devices (IUD) and levonorgestrel intrauterine delivery system (LNG-IUS).

## Summary

The EURAS-IUD study showed:

- The observed rate of uterine perforation with IUCs was low, occurring in approximately 1 in every 1000 insertions.
- The most important risk factors for uterine perforation were breastfeeding at the time of insertion and insertion in the 36 weeks after giving birth, regardless of the type of IUC inserted (see Table 1).
- IUC has a high contraceptive effectiveness: The study reaffirmed that the benefits of IUC continues to outweigh the risks for most women, including those who are breastfeeding or have recently given birth.

- Before inserting IUC, inform the user that perforation occurs in approximately 1 in every 1000 insertions and that the symptoms include:
  - severe pelvic pain after insertion (worse than period cramps)
  - not being able to feel the threads
  - pain or increased bleeding after insertion which continues for more than a few weeks
  - sudden changes in periods' characteristics
  - pain during sex

Explain to users how to check their threads and tell them to return for a check-up if they cannot feel them, especially if they also have significant pain.
Partial perforation may have occurred even if the threads can still be seen; consider this if there is severe pain following insertion and perform an ultrasound.

## Further information

Intrauterine contraception includes the copper intrauterine device (IUD) and levonorgestrel-releasing intrauterine system (LNG-IUS). IUC is used for long-term contraception. Some LNG-IUS are also licensed for other gynaecological conditions including:

- heavy menstrual bleeding
- protection from endometrial hyperplasia during estrogen replacement therapy

Uterine perforation is a complication of many gynaecological diagnostic, therapeutic and other procedures, including placement of IUC. Perforation of the body of the uterus or cervix most often occurs during IUC insertion, but might not be detected until sometime later, and may decrease the effectiveness of IUC. In this case, such a system must be removed and surgery may be required.

Summary of the EURAS-IUD study:
EURAS-IUD was a large prospective, comparative, non-interventional cohort study of women who use IUC, including LNG-IUS with initial release rate of 20mcg/24 hours LNG-IUS (Mirena) and copper IUD[1,2]. The primary outcome was uterine perforations onset.

The EURAS-IUD study was carried out in 6 European countries and included over 61,000 women (>43,000 women using LNG-IUS and >18,000 women using various brands of copper IUDs). The incidence rate of uterine perforation was 1.3 (95% CI: 1.1 - 1.6) per 1000 insertions in the whole study population, with no relevant difference between the study cohorts (1.4 [95% CI: 1.1 - 1.8] per 1000 insertions in the LNG-IUS cohort and 1.1 [95% CI: 0.7 - 1.6] per 1000 insertions in the copper IUD cohort).

The risk of perforation was independently increased in the following instances (see Table 1):
- in users who were breastfeeding (compared with women not breastfeeding) at the time of insertion
- when the IUS or IUD was inserted up to 36 weeks after giving birth).

These risk factors were independent of the type of IUC used.

Table 1: EURAS-IUD: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding and time since delivery at insertion

| | Breastfeeding at time of insertion | Not breastfeeding at time of insertion |
|---|---|---|
| Insertion ≤ 36 weeks after delivery | 5.6 per 1000 (95% CI: 3.9-7.9, n=6,047 insertions) | 1.7 per 1000 (95% CI: 0.8-3.1, n=5,927 insertions) |
| Insertion > 36 weeks after delivery | 1.6 per 1000 (95% CI: 0.0-9.1, n=608 insertions) | 0.7 per 1000 (95% CI: 0.5-1.1, n=41,910 insertions) |

The majority of perforations in both the LNG-IUS and copper IUD cohorts presented clinically as pain or bleeding. However, in 22.0% of the cases the perforation was found at a routine check-up in apparently asymptomatic women. In both cohorts, more than 50% of the perforations were diagnosed within the first two months after IUC insertion.

Recommendations:
In line with Italian Guidelines on efficacy and proper use of intrauterine contraception ("Linee Guida Italiane sull'efficacia e l'uso appropriato della contraccezione intrauterina") approved by SIGO (Italian Society of Gynecology and Obstetrics), AOGOI (Italian Hospital Ostetricians and Gynecologist Association) e AGUI (Italian Universitary Gynecologist Association)[3] must be advised women considering long-term contraception on all the available options (including LNG-IUSs and IUDs). Inform them of the benefits and risks associated to the various types of treatment, for example the possibility of intrauterine perforation with IUC, as well as the signs and symptoms of perforation to watch out for, as per the Patient Information Leaflet.

In case of a difficult insertion of the device (e.g. exceptional pain or bleeding during or after insertion) a physical examination and ultrasound must be performed immediately to exclude perforation. Physical examination alone (including checking of threads) may not be sufficient to exclude partial perforation, which may have occurred even if the threads can still be seen.

Explain to users how to check their threads and tell them to return for a check-up if they cannot feel them, especially if they also have pain, or if they have any other symptoms associable to intrauterine perforation. Remind users that during these gynaecological check-up, they should tell the doctor/nurse that she has an IUC.

## Adverse Event Reporting

Please report any suspected adverse reactions to any drugs to the AIFA National Pharmacovigilance Network through:
http://www.agenziafarmaco.gov.it/it/responsabili.

# References


1) Klaas Heinemann, Suzanne Reed, Sabine Moehner, Thai Do Minh. Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. *Contraception*, 91 (4) (2015): 280–283.

2) Klaas Heinemann, Suzanne Reed, Sabine Moehner, Thai Do Minh. Risk of Uterine Perforation with Levonorgestrel-Releasing and Copper Intrauterine Devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception*, 91 (4) (2015): 274–279.

3) Arisi E., Bruni V., Di Spiezio Sardo A., Dubini V., Gubbini G. Linee guida italiane sull'efficacia e l'uso appropriato della contraccezione intrauterina It. J. Gynaecol. Obstet. 2014, 26: N.4.

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Leverkusen, 28 September 2015

**Subject:**
**Intrauterine contraceptives - update on risk of uterine Perforation - class effect**
**Information on Direct Healthcare Professional Communication (DHPC) in Portugal**

Products concerned:
Mirena (Reg. No.: 30495.00.00; 2130495);
Mirena Duplicate (Reg. No.: 41880.00.00; ENR: 2141880)
Jaydess (Reg. No.: 86537.00.00; ENR: 2186537)
Nova T 380 (CE 0344)

Dear Madam/Sir,

In our objective to keep you continuously informed about worldwide regulatory actions regarding our products we wish to inform you herewith about the decision of the Portuguese health authority (Infarmed) to request Bayer to distribute a "Direct Healthcare Professional Communication" (DHPC) to Healthcare Professionals (HCPs) in Portugal for the intrauterine contraceptives (IUCs) Mirena, Jaydess and Nova T 380.

The DHPC was distributed to HCPs in Portugal on 27th August 2015 as agreed with Infarmed.

The DHPC informs HCPs in Portugal about the updated information regarding uterine perforation associated with the use of intrauterine devices. The updated information is based on the finalized report of the "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD). The final data showed that there is a higher risk of uterine perforation in breastfeeding women and also in women who are up to 36 weeks post-partum at the time of insertion for both levonorgestrel-intrauterine system (LNG-IUS) and copper IUDs (Cu IUDs). The DHPC also informs about incidences of perforation for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women). In addition, the DHPC provides a summary of the EURAS-IUD.

Furthermore, the DHPC advises HCPs to take this information into consideration when selecting IUCs for use in patients who are less than 36 weeks post-partum or breastfeeding at the time of insertion. Healthcare professionals are also encouraged to inform patients on the risks of uterine perforation before the procedure. Patients should be educated on self-check for the removal threads of IUCs and possible signs of this complication.

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The DHPC is enclosed for your information.

**Background**

In **Portugal,** Mirena is approved since December 1996 and the product was launched in October 1997. Approved indications for Mirena are contraception and idiopathic menorrhagia. Jaydess is approved since June 2013 and the product was launched in January 2015. Jaydess is approved for contraception. Nova T 380 is a medical device for contraception and launched since March 1999.

In March 2015 an **European Union (EU)** wide labeling variation procedure for Mirena and Jaydess related to EURAS-IUD ended positively. An additional outcome of the procedure was that Member States could decide to ask for "Direct Healthcare Professional Communication" (DHPC) regarding risk of uterine perforation if considered appropriate in a particular Member State. There was no pan-EU communication decided upon. To date, some EU countries have contacted Bayer with respect to the potential for a DHPC. Bayer has responded to these requests with its position that the other communication tools that Bayer intends to use, in addition to the updated product labeling, are most appropriate to communicate the safety information deriving from the results of the EURAS-IUD study. The health authorities in the Czech Republic, Germany, Denmark, Italy, Portugal, Slovenia, Spain and the United Kingdom disagreed with Bayer's opinion and requested that a national DHPC be issued.

Outside of the EU, the health authorities in Egypt, Hong Kong, Serbia, Singapore and South Africa requested that a DHPC related to EURAS-IUD be issued.

Based on the outcome of the EURAS-IUD study the product labeling for the medical devices Nova T 200 and Nova T 380 was also updated. The relevant labeling notifications were distributed to health authorities worldwide as appropriate. The Notified Body responsible for the CE marking in the EU (DEKRA) approved these labeling notifications on 30th June 2014.

**Company position**

EURAS-IUD is a large prospective, comparative, non-interventional cohort study in IUC users, including LNG-IUS (Mirena) and copper IUDs, with primary outcome of uterine perforations.

Uterine perforation is a complication associated with many gynaecological diagnostic, therapeutic and other procedures, including placement of IUCs. The risk of uterine perforation is not product-specific but can be considered a class effect of all IUCs currently marketed. The risk of uterine perforation, including risk factors such as breastfeeding and recent delivery, is explicitly described in the product information of all intrauterine devices. These product information have been continuously updated as new data on this risk have become available. Local SmPCs and PLs were updated accordingly.

Bayer is continuously monitoring the safety data of its intrauterine contraceptives. While providing further insight in the known risk of uterine perforation and its risk factors, the recently finalized study report of EURAS-IUD does not give rise to a new safety concern and reaffirms the positive benefit risk profile of intrauterine contraceptives. This is also the case for breast-feeding women and women who have recently delivered. Bayer considers that the final results of EURAS-IUD, while providing more detailed information on risk groups for uterine perforation, have neither changed the overall benefit-risk balance of their intrauterine contraceptives nor their condition of use.

Yours sincerely,

[redacted]

20th August 2015

# Intrauterine contraceptives (Copper IUDs – Nova T 380 - and Levonorgestrel Intrauterine delivery systems – Mirena and Jaydess) - Update on risk of uterine perforation

Dear Healthcare Professional,

Bayer would like to provide you with an update on recent data regarding risk of uterine perforation associated with the use of intrauterine contraceptives (IUC), including Copper IUDs and levonorgestrel intrauterine delivery systems (LNG-IUS)

## Summary

The "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD) study showed:

- The observed rate of uterine perforation with IUCs was low, occurring around 1 per 1000 insertions.
- The risk of uterine perforation is increased in women whose insertion is made during breastfeeding or up to 36 weeks after giving birth, independently of the type of IUC inserted.Women that use IUCs should be examined 4-12 weeks after the insertion and at least once a year.
- Intrauterine perforation may not be detected until some time after insertion.
- Before inserting the IUC you shall inform the patient of the risk of uterine perforation and advise them to seek medical help if they feel any of the following symptoms:
    - Severe pain (such as menstrual cramps) or more pain that is expected.
    - Heavy bleeding (after insertion)
    - Pain or bleeding that continues for more than a few weeks
    - Sudden changes in the menstrual periods
    - Pain during sex
    - Fail to feel the IUC wires.

The study reaffirms the positive benefit-risk profile of these medicines.

## Further information on the safety concern and the recommendations

Summary of the EURAS-IUD study:

EURAS-IUD is a large prospective, comparative, non-interventional cohort study in IUC users, including and LNG-IUS and IUC, with primary outcome of uterine perforations.

The EURAS-IUD study was carried out in 6 European countries and included over 61,000 IUC users (>43,000 women using LNG-IUS and >18,000 women using various brands of copper IUDs). The

incidence rate of uterine perforation was 1.3 (95% CI: 1.1 - 1.6) per 1000 insertions in the whole study population, with no relevant difference between the study cohorts (1.4 [95% CI: 1.1 - 1.8] per 1000 insertions in the LNG-IUS cohort and 1.1 [95% CI: 0.7 - 1.6] per 1000 insertions in the copper IUD cohort).

EURAS-IUD showed that breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 1). These risk factors were independent of the type of IUC inserted.

Table 1: EURAS-IUD: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding and time elapsed since delivery at insertion

| | Breastfeeding at time of insertion | Not breastfeeding at time of insertion |
|---|---|---|
| Insertion ≤ 36 weeks after delivery | 5.6 per 1000 (95% CI: 3.9-7.9, n=6,047 insertions) | 1.7 per 1000 (95% CI: 0.8-3.1, n=5,927 insertions) |
| Insertion > 36 weeks after delivery | 1.6 per 1000 (95% CI: 0.0-9.1, n=608 insertions) | 0.7 per 1000 (95% CI: 0.5-1.1, n=41,910 insertions) |

No serious sequelae were associated with any of the perforations in the study. The majority of perforations presented symptoms as pain or bleeding problems. In both cohorts, more than 50% of the perforations were diagnosed within the first two months after IUC insertion.

Recommendations:

Patient counselling on available contraceptive options should include information on medicine benefits and risks (eg. uterine perforation), as well as the signs and symptoms of perforation as described in the patient information leaflet.

In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation. Physical examination alone (including checking of threads) may not be sufficient to exclude partial perforation. Women using IUCs should have a post-insertion check-up 4-12 weeks after placement, and at least annually thereafter.

Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of IUCs. Such a system must be removed as soon as possible, surgery may be required.You should teach the patient how to check the wires of the IUC and inform her that she should seek medical advice if she is not able to feel the wires.

## Call for reporting

*INFARMED pharmacovigilance contact details*

## Company contact point

*Bayer Portugal contact details*

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Jenapharm GmbH & Co. KG • D-07740 Jena

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Leverkusen, 28 September 2015

**Subject:**
**Intrauterine contraceptives - update on risk of uterine Perforation - class effect**
**Information on Direct Healthcare Professional Communication (DHPC) in Slovenia**

Products concerned:
Mirena (Reg. No.: 30495.00.00; 2130495);
Mirena Duplicate (Reg. No.: 41880.00.00; ENR: 2141880)
Jaydess (Reg. No.: 86537.00.00; ENR: 2186537)

Dear Madam/Sir,

In our objective to keep you continuously informed about worldwide regulatory actions regarding our products we wish to inform you herewith about the decision of the Slovenian health authority (JAZMP) to request Bayer to distribute a "Direct Healthcare Professional Communication" (DHPC) to Healthcare Professionals (HCPs) in Slovenia for the intrauterine contraceptives (IUCs) Mirena and Jaydess. There is no parallel request for copper intrauterine devices (Cu IUDs).

The DHPC was distributed to HCPs in Slovenia on 7th September 2015 as agreed with JAZMP.

The DHPC informs HCPs in Slovenia about the updated information regarding uterine perforation associated with the use of intrauterine devices. The updated information is based on the finalized report of the "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD). The final data showed that there is a higher risk of uterine perforation in breastfeeding women and also in women who are up to 36 weeks post-partum at the time of insertion for both levonorgestrel-intrauterine system (LNG-IUS) and copper IUDs (Cu IUDs). The DHPC also informs about incidences of perforation for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women). In addition, the DHPC provides a summary of the EURAS-IUD.

Furthermore, the DHPC advises HCPs to take this information into consideration when selecting IUCs for use in patients who are less than 36 weeks post-partum or breastfeeding at the time of insertion. Healthcare professionals are also encouraged to inform patients on the risks of uterine perforation

before the procedure. Patients should be educated on self-check for the removal threads of IUCs and possible signs of this complication.

The DHPC is enclosed for your information.

**Background**

In **Slovenia**, Mirena is approved since May 1999 and the product was launched in October 1999. Approved indications for Mirena are contraception and idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy. Jaydess is approved since March 2013 and the product was launched in January 2014. Jaydess is approved for contraception.

In March 2015 an **European Union (EU)** wide labeling variation procedure for Mirena and Jaydess related to EURAS-IUD ended positively. An additional outcome of the procedure was that Member States could decide to ask for "Direct Healthcare Professional Communication" (DHPC) regarding risk of uterine perforation if considered appropriate in a particular Member State. There was no pan-EU communication decided upon. To date, some EU countries have contacted Bayer with respect to the potential for a DHPC. Bayer has responded to these requests with its position that the other communication tools that Bayer intends to use, in addition to the updated product labeling, are most appropriate to communicate the safety information deriving from the results of the EURAS-IUD study. The health authorities in the Czech Republic, Germany, Denmark, Italy, Portugal, Slovenia, Spain and the United Kingdom disagreed with Bayer's opinion and requested that a national DHPC be issued.

Outside of the EU, the health authorities in Egypt, Hong Kong, Serbia, Singapore and South Africa requested that a DHPC related to EURAS-IUD be issued.

**Company position**

EURAS-IUD is a large prospective, comparative, non-interventional cohort study in IUC users, including LNG-IUS (Mirena) and copper IUDs, with primary outcome of uterine perforations.

Uterine perforation is a complication associated with many gynaecological diagnostic, therapeutic and other procedures, including placement of IUCs. The risk of uterine perforation is not product-specific but can be considered a class effect of all IUCs currently marketed. The risk of uterine perforation, including risk factors such as breastfeeding and recent delivery, is explicitly described in the product information of all intrauterine devices. These product information have been continuously updated as new data on this risk have become available. Local SmPCs and PLs were updated accordingly.

Bayer is continuously monitoring the safety data of its intrauterine contraceptives. While providing further insight in the known risk of uterine perforation and its risk factors, the recently finalized study report of EURAS-IUD does not give rise to a new safety concern and reaffirms the positive benefit risk profile of intrauterine contraceptives. This is also the case for breast-feeding women and women who have recently delivered. Bayer considers that the final results of EURAS-IUD, while providing more detailed information on risk groups for uterine perforation, have neither changed the overall benefit-risk balance of their intrauterine contraceptives nor their condition of use.

Yours sincerely,

[redacted]

**Direct Healthcare Professional Communication**

Date: 7 September 2015

**Intrauterine device (IUD): update on the risk of uterine perforation**

Ladies and Gentlemen,

In agreement with the Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP), we would like to inform you of the latest findings from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD). This was a large prospective, comparative, non-interventional cohort study of women using intrauterine devices (IUD). The study investigated the use of copper-containing intrauterine devices (Cu-IUD) and levonorgestrel-containing intrauterine devices, also known as intrauterine systems (LNG-IUS).

**Summary:**

The EURAS-IUD study showed the following findings:

- The observed rate of uterine perforation with both types of intrauterine device was low, occurring in approximately 1 per 1,000 insertions.

- The most important risk factors for uterine perforation were breastfeeding at the time of insertion and insertion in the first 36 weeks after giving birth (see Table 1). Both risk factors were independent of the type of intrauterine device inserted.

- Intrauterine devices have high contraceptive effectiveness. The study reaffirmed that the benefits of intrauterine device outweigh the risks, also in women who are breastfeeding or have recently given birth.

The following will be recommended to prescribing doctors:

- Before inserting an intrauterine device, inform the user that uterine perforation occurs in approximately 1 per 1,000 insertions and may be associated with the following signs and symptoms:
    - severe pain in the lower abdomen after insertion (worse than period cramps)
    - threads can no longer be felt in the vagina

    - pain or increased menstrual bleeding after insertion which continues for more than a couple of weeks
    - sudden changes in periods
    - pain during sex
- Instruct users on how to check for the present of the threads in the vagina and advise them to return for a check-up if they cannot feel the threads (especially if exceptional pain occurs).
- Bear in mind that partial perforation may have occurred even if the threads can still be seen or felt. Consider this in particular if there is severe pain following insertion and perform an ultrasound.

**Further information**

Intrauterine contraception includes the levonorgestrel-releasing intrauterine system (LNG-IUS) and copper intrauterine device (Cu-IUD). Both forms of intrauterine devices are used for long-term contraception. Some IUD are also licensed for other gynaecological indications including:

- hypermenorrhea
- emergency contraception.

Uterine perforation is a possible complication of many diagnostic or therapeutic intrauterine procedures and may likewise occur with insertion of an intrauterine device. Perforation of the body of the uterus or cervix most often occurs during IUD insertion, but might not be detected until some time later. As a result the effectiveness of intrauterine devices may be reduced. In such cases, the intrauterine device must be removed immediately. A surgery may be required.

**Summary of the EURAS-IUD study:**

The EURAS-IUD study was a large prospective, comparative, non-interventional cohort study of IUD users, including both users of copper-containing IUD and users of LNG-IUS with an initial release rate of 20 mcg/24 hours (Mirena). The primary outcome of the study was to investigate the rate of uterine perforation. The EURAS-IUD study was carried out in 6 European countries and included 61,000 women (> 43,000 women using LNG-IUS and > 18,000 women using copper-containing IUD (various brands)). The incidence rate of uterine perforation was 1.3 (95% CI: 1.1 – 1.6) per 1,000 insertions in the whole study population, with no relevant difference between the study cohorts (1.4 (95% CI: 1.1 – 1.8) per 1,000 insertions in the LNG-IUS cohort and 1.1 (95% CI: 0.7 – 1.6) per 1,000 insertions in the cohort of women with copper-containing IUD.

The risk of perforation was independently increased in the following instances (see Table 1):

- in women who were breastfeeding at the time of insertion (compared with women not breastfeeding),
- in women in whom IUD insertion took place in the first 36 weeks after giving birth (compared with insertion more than 36 weeks after giving birth).

Both risk factors were independent of the type of the intrauterine device inserted.

Table 1

Incidence of perforation per 1,000 insertions for the entire study cohort, stratified by breastfeeding/not breastfeeding at the time of insertion and time from delivery to insertion (women after birth)

| | **breastfeeding at time of insertion** | **not breastfeeding at time of insertion** |
|---|---|---|
| **insertion ≤ 36 weeks after delivery** | 5.6 per 1,000 (95% CI: 3.9 – 7.9; n = 6,047 insertions) | 1.7 per 1,000 (95% CI: 0.8 – 3.1; n = 5,927 insertions) |
| **insertion > 36 weeks after delivery** | 1.6 per 1,000 (95% CI: 0.0 – 9.1; n = 608 insertions) | 0.7 per 1,000 (95% CI: 0.5 – 1.1; n = 41,910 insertions) |

The perforations that occurred during the study were not associated with serious sequelae, such as bowel or bladder injury, generalised septicaemia or peritonitis. The majority of perforations in both the LNG-IUS cohort and the cohort of women with copper-containing IUD presented clinically as pain or bleeding problems. However, in 22% of the cases, the perforation was found at a routine check-up in apparently asymptomatic users. In both cohorts, more than 50% of the perforations were diagnosed within the first two months of insertion of the intrauterine device.

**Recommendations**

Users who are considering long-term contraception should be informed of the risks and benefits of this method. This includes information on the risk and signs of perforation. These are also described in the package leaflet.

In case of a difficult insertion (e.g. exceptional pain or bleeding during or after insertion) perform a physical examination including ultrasound immediately to exclude perforation. Physical examination alone (including checking of threads) might not be sufficient to exclude partial perforation, which may have occurred even if the threads can still be seen or felt.

Users should receive instruction in how to check the presence of the threads and should be made aware to return for a check-up if the threads cannot be felt (especially if exceptional pain occurs) or if any other signs and symptoms of perforation occur (see list in above summary). In addition, users should be reminded to inform the doctor during these check-ups of the presence of the intrauterine device (in case he/she is not the doctor that inserted the device).

**Reporting of side effects**

Please report all suspected cases of adverse drug reactions associated with the use of intrauterine devices immediately, in accordance with the provisions of the Rules on pharmacovigilance of medicinal products for human use (Official Gazette of the Republic of Slovenia No 57/14) and as described on the website www.jazmp.si.

Please send the completed report on suspected cases of adverse drug reactions to the national pharmacovigilance centre: Univerzitetni klinični center Ljubljana, Interna klinika, Center za zastrupitve, Zaloška cesta 2, SI-1000 Ljubljana, fax: + 386 (0)1 434 76 46 or email: farmakovigilanca@kclj.si

**Contacts**

Should you have any further questions or require additional information, please contact:

Bayer d.o.o., Bravničarjeva ulica 13, 1000 Ljubljana

phone: 1 58 14 400

fax: 1 58 14 403

email: info.si@bayer.com

Best regards,

Lucija Zlodi Gošnik, MPharm

Head of Medical Department

Jenapharm

Jenapharm GmbH & Co. KG • D-07740 Jena

[redacted]

[redacted]

Leverkusen, 28 September 2015

**Subject:**
**Intrauterine contraceptives - update on risk of uterine Perforation - class effect**
**Information on Direct Healthcare Professional Letter (DHPCL) in Hong Kong**

Products concerned:
Mirena (Reg. No.: 30495.00.00; 2130495);
Mirena Duplicate (Reg. No.: 41880.00.00; ENR: 2141880)

Dear Madam/Sir,

In our objective to keep you continuously informed about worldwide regulatory actions regarding our products we wish to inform you herewith about the decision of the Department of Health (DH) in Hong Kong to distribute a "Dear Healthcare Professional Letter" (DHCPL) to Healthcare Professionals (HCPs) in Hong Kong for the intrauterine contraceptive (IUC) Mirena.

The DHCPL is dated 29 June 2015 and was distributed to Healthcare Professionals in Hong Kong by the DH.

The DHCPL informs HCPs in Hong Kong about the updated information regarding uterine perforation associated with the use of intrauterine devices. The updated information is based on the finalized report of the "European Active Surveillance Study for Intrauterine Devices" (EURAS-IUD). The final data showed that there is a higher risk of uterine perforation in breastfeeding women and also in women who are up to 36 weeks post-partum at the time of insertion for both levonorgestrel-intrauterine system (LNG-IUS) and copper IUDs (Cu IUDs). The DHCPL also informs about incidences of perforation for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women). In addition, the DHCPL provides a summary of the EURAS-IUD.

Furthermore, the DHCPL advises HCPs to take this information into consideration when selecting IUCs for use in patients who are less than 36 weeks post-partum or breastfeeding at the time of insertion. Healthcare professionals are also encouraged to inform patients on the risks of uterine perforation before the procedure. Patients should be educated on self-check for the removal threads of IUCs and possible signs of this complication.

Jenapharm

The DHCPL is enclosed for your information.

**Background**

In **Hong Kong**, Mirena is approved since August 1996 and the product was launched in February 1998. Approved indications for Mirena are contraception, idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy.

In March 2015 an **European Union (EU)** wide labeling variation procedure for Mirena related to EURAS-IUD ended positively. An additional outcome of the procedure was that Member States could decide to ask for "Direct Healthcare Professional Communication" (DHPC) regarding risk of uterine perforation if considered appropriate in a particular Member State. There was no pan-EU communication decided upon. To date, some EU countries have contacted Bayer with respect to the potential for a DHPC. Bayer has responded to these requests with its position that the other communication tools that Bayer intends to use, in addition to the updated product labeling, are most appropriate to communicate the safety information deriving from the results of the EURAS-IUD study. The health authorities in the Czech Republic, Germany, Denmark, Italy, Portugal, Slovenia, Spain and the United Kingdom disagreed with Bayer's opinion and requested that a national DHPC be issued.

Outside of the EU, the health authorities in Egypt, Hong Kong, Serbia, Singapore and South Africa requested that a DHPC/DHCPL related to EURAS-IUD be issued.

**Company position**

EURAS-IUD is a large prospective, comparative, non-interventional cohort study in IUC users, including LNG-IUS (Mirena) and copper IUDs, with primary outcome of uterine perforations.

Uterine perforation is a complication associated with many gynaecological diagnostic, therapeutic and other procedures, including placement of IUCs. The risk of uterine perforation is not product-specific but can be considered a class effect of all IUCs currently marketed. The risk of uterine perforation, including risk factors such as breastfeeding and recent delivery, is explicitly described in the product information of all intrauterine devices. These product information have been continuously updated as new data on this risk have become available. Local SmPCs and PLs were updated accordingly.

Bayer is continuously monitoring the safety data of its intrauterine contraceptives. While providing further insight in the known risk of uterine perforation and its risk factors, the recently finalized study report of EURAS-IUD does not give rise to a new safety concern and reaffirms the positive benefit risk profile of intrauterine contraceptives. This is also the case for breast-feeding women and women who have recently delivered. Bayer considers that the final results of EURAS-IUD, while providing more detailed information on risk groups for uterine perforation, have neither changed the overall benefit-risk balance of their intrauterine contraceptives nor their condition of use.

Yours sincerely,

[redacted]

衞生署藥物辦公室
藥物註冊及進出口管制部

香港九龍南昌街 382 號公共衞生檢測中心三樓

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**DEPARTMENT OF HEALTH**
**DRUG OFFICE**
**DRUG REGISTRATION AND IMPORT/EXPORT CONTROL DIVISION**
3/F., Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon, Hong Kong

(來函請敍明此檔案號碼)
(IN REPLY PLEASE QUOTE THIS FILE REF.)

29 June 2015

Dear Healthcare Professionals,

**Intrauterine contraception: uterine perforation - updated information on risk factors**

Your attention is drawn to the Medicine and Healthcare products Regulatory Agency's (MHRA) announcement regarding updated information on risk factors for uterine perforation in intrauterine contraception.

The European Active Surveillance Study for Intrauterine Devices (EURAS-IUD) was an observational study which examined the risk of uterine perforation with intrauterine contraception. The study followed 43,078 women who used levonorgestrel-releasing intrauterine systems (IUSs) and 18,370 women who used copper intrauterine devices (IUDs). The results revealed that the risk of perforation was increased in women who were lactating (compared with women not lactating) at the time of insertion, or when the IUS or IUD was inserted up to 36 weeks (compared with more than 36 weeks) after giving birth.

The MHRA found that the benefits of intrauterine contraception still strongly outweigh the rare risk of perforation for most women, including those who are lactating or have recently given birth. Therefore the MHRA has not put in place any new restrictions on use of intrauterine contraception based on the study findings. The summaries of product characteristics and patient information leaflets in the UK have been updated.

Healthcare professionals are advised of the following:

- Before inserting an IUS or IUD, inform women that perforation occurs in less than 1 in 1,000 women and that the symptoms include:
  - severe pelvic pain after insertion (worse than period cramps)
  - pain or heavy bleeding after insertion which continues for more than a few weeks
  - sudden changes in periods
  - pain during sex
  - not being able to feel the threads
- Explain to women how to check their threads and tell them to return for a check-up if they cannot feel them (especially if they also have significant pain). As partial perforation may have occurred even if the threads can still be seen. Consider this if there is severe pain following insertion.

Please refer to the MHRA's website for details:

https://www.gov.uk/drug-safety-update/intrauterine-contraception-uterine-perforation-updated-information-on-risk-factors

In Hong Kong, there is one registered pharmaceutical product which is an IUS, namely Mirena Intrauterine system 52mg (HK-41251) which contains levonorgestrel. It is a prescription-only medicine registered by Bayer Healthcare Ltd (Bayer). So far, the Department of Health (DH) has not received any adverse drug reaction report on the product. Bayer has submitted an application to the DH to update the package insert of the product to include the relevant warning, and the application is under evaluation. In view of the MHRA's announcement, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. The DH will remain vigilant on any safety updates of the drug. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

[redacted]