Healthcare Professional Brochure describing the risk of Ectopic Pregnancy

and

how to differentiate between Bayer Levonorgestrel Intra-Uterine Systems (LNG-IUS)

May 2021

The aim of this brochure is to give further information on ectopic pregnancy in association with the use of Bayer Levonorgestrel Intra-Uterine Systems (LNG-IUS) – Jaydess®▼ 13.5 mg intrauterine delivery system, Kyleena® 19.5mg intrauterine delivery system and Mirena® 52mg intrauterine delivery system. In addition, it explains the differences between the three different LNG-IUS to reduce the risk of medication error.

Sections:

1. Ectopic pregnancy

a. Rate
b. Symptoms and signs
c. Risk Factors
d. Impact of ectopic pregnancy of future fertility
e. Contraceptive counselling and ectopic pregnancy

2. Differentiation of Mirena®, Kyleena® and Jaydess®▼

a. Licensed Indications
b. Pharmaceutical form and release rate
c. Physical appearance
d. X Ray and ultrasound images

Before inserting a Bayer LNG-IUS, the patient information leaflet in the package should be given to the woman for her to read. A patient reminder card is also included in every pack. Please bring this to the woman's attention, so that relevant information can be noted on the card, i.e., insertion date and latest date for removal in line with the duration of use in the indication.

▼ Jaydess is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to HPRA Pharmacovigilance,
Website: **www.hpra.ie**

Adverse events or quality complaints should also be reported to Bayer Limited Drug Safety on 01-216 3300 or alternatively by email at **adr-ireland@bayerhealthcare.com**

For further information and additional details on Kyleena, Jaydess▼ or Mirena, please see the Summary of Product Characteristics (SmPC) on **www.medicines.ie**

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1. Ectopic Pregnancy in Women using LNG-IUS

a. Rate

The absolute rate of ectopic pregnancy observed in women using LNG-IUS is low since they have high contraceptive efficacy. However, in the event that a woman becomes pregnant while using an LNG-IUS, there is an approximately 50% chance that the pregnancy will be ectopic.

Mirena:
In Mirena clinical trials in the indication contraception, the Pearl Index was approximately 0.2 at 1 year and the cumulative failure rate was approximately 0.7% at 5 years. During year 6 of Mirena use, the Pearl Index was 0.35 [95% CI (0.01; 1.95)].

The absolute rate of ectopic pregnancies with Mirena was approximately 0.1% per year.

Jaydess:
In Jaydess clinical trials, the 1-year Pearl Index was 0.41 (95% confidence limits 0.13 – 0.96) and the 3-years Pearl Index was 0.33 (95% confidence limits 0.16 – 0.60). The failure rate was approximately 0.4% at 1 year and the cumulative failure rate was approximately 0.9% at 3 years. The overall incidence of ectopic pregnancy in clinical trials was approximately 0.11 per 100 woman-years.

Kyleena:
In Kyleena clinical trials, the 1-year Pearl Index was 0.16 (95% confidence limits 0.02 – 0.58) and the 5-years Pearl Index was 0.29 (95% confidence limits 0.16 – 0.50). The failure rate was approximately 0.2% at 1 year and the cumulative failure rate was approximately 1.4% at 5 years. The overall incidence of ectopic pregnancy was approximately 0.20 per 100 women-years.

The studies on the background incidence of ectopic pregnancy based on data from two large managed care databases in the US have estimated ectopic pregnancy rates in the range of 1.7–2.5% [i] of all pregnancies or 0.11 - 0.23 per 100 woman-years in women aged 20–39 in the general population (including contraceptive users and non-users).[ii, iii]

b. Signs and Symptoms of Ectopic Pregnancy

It is important that the signs and symptoms of ectopic pregnancy are recognised at the earliest opportunity so that treatment can be prompt. It is therefore important to counsel the woman on the signs and symptoms of ectopic pregnancy which include:[iv, v]

- Pain on one side of the lower abdomen, which may be severe or persistent. The pain may develop suddenly and sharply or may gradually worsen over several days
- Vaginal bleeding. This may be different to that associated with menses (e.g. the blood may be darker)
- Persistent bleeding that occurs after a period of amenorrhoea, particularly if the bleeding is associated with pain
- "Normal" symptoms of pregnancy but with bleeding and a feeling of dizziness
- Shoulder-tip pain (owing to blood leaking into the abdomen and irritating the diaphragm)
- Severe pain or collapse as a result of heavy internal bleeding associated with rupture
- General symptoms: diarrhoea, feeling faint or pain on passing faeces; these would only be cause for concern if they occurred in addition to any of the more specific symptoms above
- A positive pregnancy test

If a woman has a positive pregnancy test while using an LNG-IUS, the possibility of ectopic pregnancy should be considered, and further tests should be performed to either exclude or diagnose ectopic pregnancy. [i]

Early diagnosis of ectopic pregnancy can be difficult, and a series of investigations may be necessary. Ectopic pregnancy may be confirmed by transvaginal ultrasound scan and by a ßhCG blood test. [vi]

c. Risk Factors for Ectopic Pregnancy

Risk factors for ectopic pregnancy include: [vi, vii]

- Prior ectopic pregnancy
- Age (risk increases with advancing age)
- Smoking (risk increases with increasing consumption)
- Prior spontaneous abortion or induced abortion (although another study showed no association, see footnote[†] to Table 1)
- Prior sexually transmitted disease
- Prior tubal surgery
- History of infertility
- Multiple sexual partners
- Endometriosis

A case-control study for the assessment of risk factors associated with ectopic pregnancy was conducted based on data from the ectopic pregnancy register of Auvergne (France) and associated case-controlled studies.[viii] Overall, 803 cases of ectopic pregnancy and 1,683 deliveries were included in the analysis; this provided sufficient power to comprehensively investigate all ectopic pregnancy risk factors. The main statistically significant risk factors for ectopic pregnancy by logistic regression analysis are shown in Table 1.

Table 1: Statistically significant risk factors for ectopic pregnancy by final logistic regression analysis (random effects model), register of Auvergne, France, 1993–2000 [viii]

Variables	Adjusted OR	95% CI	p value
Woman's age (Years)			
<20	0.6	0.2,2.1	
20-24	0.9	0.7, 1.3	
25-29	1		0.01
30-34	1.3	1.0,1.7	
35-39	1.4	1.0, 2.0	
≥40	2.9	1.4,6.1	
Smoking			
Never	1		<0.001
Past smoker	1.5	1.1, 2.2	
1-9 cigarettes/day	1.7	1.2, 2.4	
10-19 cigarettes/day	3.1	2.2, 4.3	
≥20 cigarettes/day	3.9	2.6, 5.9	
Prior Spontaneous abortions†			
None	1		0.02
1-2	1.2	0.9, 1.6	
≥3	3.0	1.3, 6.9	
Prior Induced abortions			
None	1		0.05
Surgical only	1.1	0.8, 1.6	
Medical (medical or surgical)	2.8	1.1, 7.2	
Prior sexually transmitted disease			
None	1		<0.001

Yes, without salpingitis	1.0	0.8, 1.3	
Yes, with probable PID‡	2.1	0.8, 5.4	
Yes, with confirmed PID§	3.4	2.4, 5.0	
Prior Tubal Surgery			
No	1		<0.001
Yes	4.0	2.6,6.1	
Previous oral contraceptive use			
No	1		0.03
Yes	0.7	0.5, 1.0	
History of infertility			
No	1		<0.001
<1 year	2.1	1.2, 3.6	
1-2 years	2.6	1.6, 4.2	
>2 years	2.7	1.8, 4.2	

Note: Only risk factors associated with a significant trend (p value) for ectopic pregnancy by logistic regression are shown.

Note: Prior ectopic pregnancy and multiple sexual partners were NOT included in the final logistic regression analysis. However, in univariate analysis: for women with 1 prior ectopic pregnancy the crude OR=12.5; for women with ≥2 prior ectopic pregnancies the crude OR=76.6, (for p <0.001 for trend); for a lifelong number of sexual partners >5, the crude OR=1.6, for a lifelong number of sexual partners 2-5, the crude OR=1.0 (p =0.003 for trend)

† No significant association with ectopic pregnancy was demonstrated for prior spontaneous abortion in another case-controlled study [viii]

‡ Probable pelvic inflammatory disease, association with fever, abdominal pain, and vaginal discharge

§ Pelvic inflammatory disease confirmed by laparoscopy and/or positive serologic tests for Chlamydia Trachomatis

CI - confidence interval

OR - odds ratio

PID - pelvic inflammatory disease

d. Impact of Ectopic Pregnancy on Future Fertility

Ectopic pregnancy can result in damage to, or the loss of, a reproductive organ (for example a fallopian tube) which in turn may have a detrimental impact on the woman's future fertility.

e. Ectopic Pregnancy and Contraceptive Counselling

Women should be counselled on the benefits and risks of all contraceptive options available, including LNG-IUS, to allow them to make an informed choice. This includes counselling on their individual risk of ectopic pregnancy while using an LNG-IUS.

Women who then choose an LNG-IUS should be educated on how to recognise the signs and symptoms of pregnancy and, in particular, ectopic pregnancy and the importance of seeking medical attention immediately if they experience any of these signs or symptoms. They should also be advised that in the unlikely event that they become pregnant while using an LNG-IUS, they should contact a healthcare provider immediately in order to exclude or diagnose ectopic pregnancy.

The healthcare provider should evaluate the risk of ectopic pregnancy for each individual woman considering an LNG-IUS as their contraceptive method of choice.

2. Differentiation of Mirena, Jaydess, and Kyleena

a. Indication of use and treatment duration

- Mirena is licensed in the indication of contraception for up to 6 years. Mirena is also licensed for the treatment of idiopathic menorrhagia, and for protection from endometrial hyperplasia during use of oestrogen replacement therapy for up to 5 years
- Jaydess is licensed in the indication of contraception for up to 3 years
- Kyleena is licensed in the indication of contraception for up to 5 years

b. Pharmaceutical form and release rate

- All three IUS are T shaped devices that are placed within the uterine cavity and provide a continuous release of levonorgestrel. The insertion technique for placement of all three IUS is identical.
- Estimated average *in vivo* LNG release rates for all 3 products are summarized in Table 2 on the next page:

Table 2: Estimated *in vivo* LNG release rates (µg/day) of the 3 LNG-IUS

	Mirena	Jaydess	Kyleena
Initial Release*	20	14	17.5
at 2 months	n/c	10	15.3
at 1 year	18	6	9.8
at the end of indicated period of use**	9	5	7.4

* For Jaydess and Kyleena determined on Day 25 post insertion, for Mirena determined shortly after insertion

** For Jaydess 3 years, for Kyleena 5 years and Mirena 6 years (for the indication contraception)
n/c not calculated

c. Physical Appearance

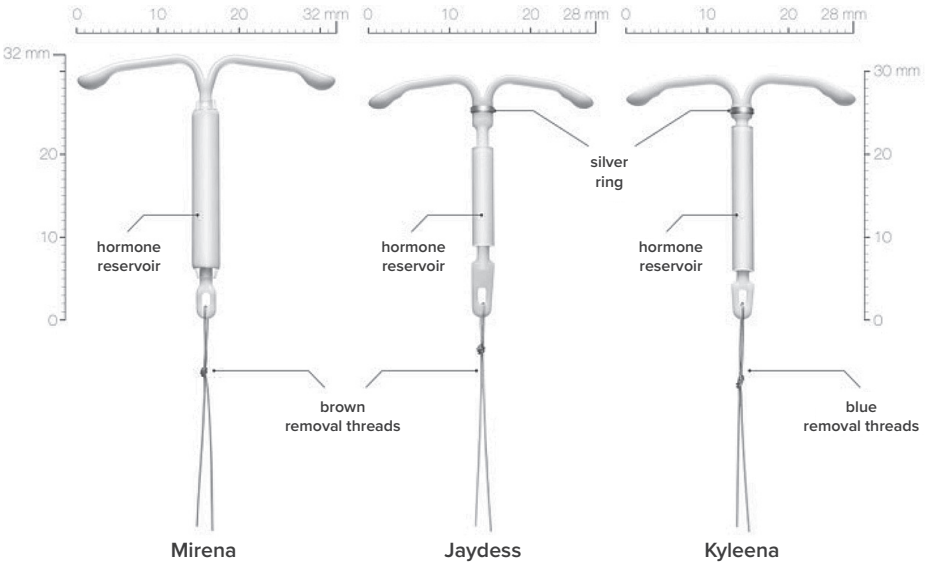

Figure 1: Physical appearance of Mirena, Jaydess, and Kyleena

- Jaydess and Kyleena are visually very similar. The upper end of the vertical stem of the T-body contains a silver ring for ultrasound (US) identification and the T-body dimensions as well as the insertion tube diameter are smaller compared to Mirena (for dimensions see Figure 1 and Table 3).

The most prominent differences between these two products are:

  - The hormone reservoir around the stem of the T-body is longer for Kyleena compared to Jaydess.
  - Jaydess: *Brown* coloured removal threads are attached to the loop at the end of the T-body stem.
  - Kyleena: *Blue* coloured removal threads are attached to the loop at the end of the T-body stem.

- Mirena has no silver ring and the T-body dimensions as well as the insertion tube diameter are bigger compared to Jaydess and Kyleena. *Brown* coloured removal threads are attached to the loop at the end of the T-body stem.

d. X-ray and Ultrasound Images

- The T-body of all three IUS contains barium sulphate which makes it visible in X-ray examination.
- Jaydess and Kyleena can be differentiated from Mirena by the silver ring that is visible in ultrasound.
- A distinction between Jaydess and Kyleena in situ per ultrasound is not possible. They can be distinguished by the different colour of the removal threads visible at the cervical os (see above).

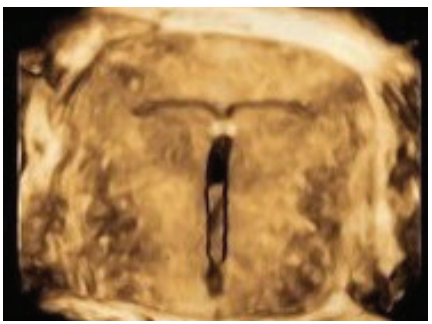

Figure 2: Kyleena – coronal plane (3D Imaging)
Source: Dr. S. Massimo Lombardo, Munich

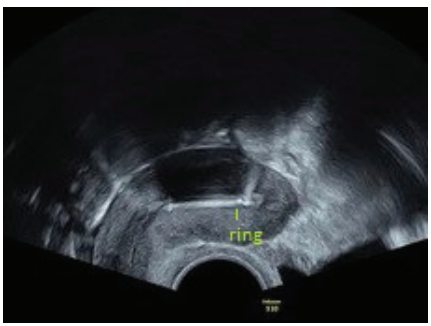

Figure 3: Kyleena – sagittal plane (2D Imaging)
Source: Dr. S. Massimo Lombardo, Munich

There is no difference in US imaging between Jaydess and Kyleena.

- Mirena has no silver ring

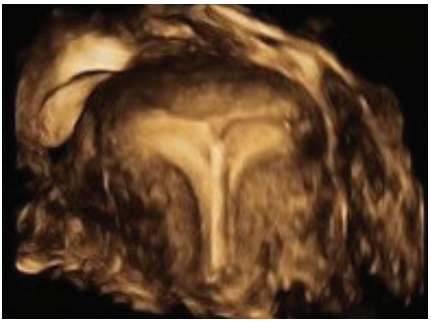

Figure 4: Mirena – coronal plane (3D Imaging)
Source: Dr. S. Massimo Lombardo, Munich

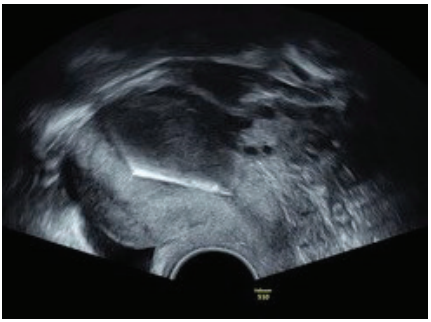

Figure 5: Mirena – sagittal plane (2D Imaging)
Source: Dr. S. Massimo Lombardo, Munich

Summary

Mirena can be distinguished from Jaydess and Kyleena by the combination of the absence of a silver ring and the brown colour of the removal threads. Mirena can be used for up to 6 years in the indication contraception, and up to 5 years in the indications idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy.

Jaydess can be distinguished from Mirena and Kyleena by the combination of the visibility of the silver ring on ultrasound and the brown colour of the removal threads. Jaydess can be used for up to 3 years in the indication contraception.

Kyleena can be distinguished from Mirena and Jaydess by the combination of the visibility of the silver ring on ultrasound and the blue colour of the removal threads. Kyleena can be used for up to 5 years in the indication contraception.

The T-body of all three IUS contains barium sulphate which makes it visible in X-ray examination.

Table 3: Overview over the differences between the 3 Bayer LNG-IUS

	Mirena	Jaydess	Kyleena
Total LNG content [mg]	52	13.5	19.5
Maximum duration of use [years]	6*	3	5
T-frame dimensions [mm]	32 x 32	28 x 30	28 x 30
Insertion tube diameter [mm]	4.40	3.80	3.80
Silver ring for improved visibility in US	no	yes	yes
Colour of removal threads	brown	brown	blue

* For the indication contraception

For differentiation of Mirena, Jaydess and Kyleena from LNG IUDs of other marketing authorization holders, please refer to the information provided for these products on the HPRA website, **www.hpra.ie**

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i Van Den Eeden SK, Shan J, Bruce C, Glasser M. Ectopic pregnancy rate and treatment utilization in a large managed care organization. Obstet Gynecol. 2005 May;105(5 Pt 1):1052-7

ii Trabert B, Holt VL, Yu O, et al. Population-based ectopic pregnancy trends, 1993-2007. Am J Prev Med. 2011 May;40(5):556-60

iii Trabert B et al: Erratum on Trabert B et al, Population-based ectopic pregnancy trends, 1993-2007. Am J Prev Med 2012;42(1):107–108

iv Torpy JM, Burke AE, Golub RM. JAMA patient page. Ectopic pregnancy. JAMA 2012;308:829

v NHS Choices, Symptoms of Ectopic Pregnancy, 2019. Available at https://www.nhs.uk/conditions/ectopic-pregnancy/symptoms/ (accessed 15 July 2019)

vi Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk EJ on behalf of the Royal College of Obstetricians and Gynaecologists. Diagnosis and management of ectopic pregnancy. BJOG 2016;.123:e15–e55

vii Bouyer J, Coste J, Shojaei T et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population based study in France. Am J Epidemiol 2003;157:185–194

viii Barnhart KT, Sammel MD, Gracia CR et al. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril 2006;86:36–43

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