

Mirena and Jaydess
Levonorgestrel IUS (LNG-IUS)

Healthcare professional Guide to describe risk of Ectopic pregnancy and how to differentiate between Bayer Levonorgestrel IUS (LNG-IUS)

The aim of this guide is to give further information on ectopic pregnancy in association with the use of Bayer LNG-IUS. In addition, it explains the differences between the two different LNG-IUS to reduce the risk of medication error.

Table of Contents:

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® 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.

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.

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

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.

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%¹ 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).^{2,3}

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:^{4,5}

- 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

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

- 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. ¹

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 β hCG blood test. ⁶

c. Risk Factors for Ectopic Pregnancy

Risk factors for ectopic pregnancy include: ^{6,7}

- 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.⁸ 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.

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

Table 1: Statistically significant risk factors for ectopic pregnancy by final logistic regression analysis (random effects model), register of Auvergne, France, 1993–2000⁸

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	

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

≥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

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

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 study⁸

‡ 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

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

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 and Jaydess.

a. Indication of use and treatment duration

- Mirena is inserted into the uterine cavity and is effective for 6 years in the indication contraception and 5 years in the indications idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.
- Jaydess is licensed in the indication of contraception for up to 3 years.

b. Pharmaceutical form and release rate

- Both 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 both IUS is identical.
- Estimated average *in vivo* LNG release rates for both products are summarized in Table 2 below:

Table 2: Estimated *in vivo* LNG release rates ($\mu\text{g}/\text{day}$) of the 2 LNG-IUS

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

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

** For Jaydess 3 years and Mirena 6 years (for the indication contraception)

n/c not calculated

c. Physical Appearance

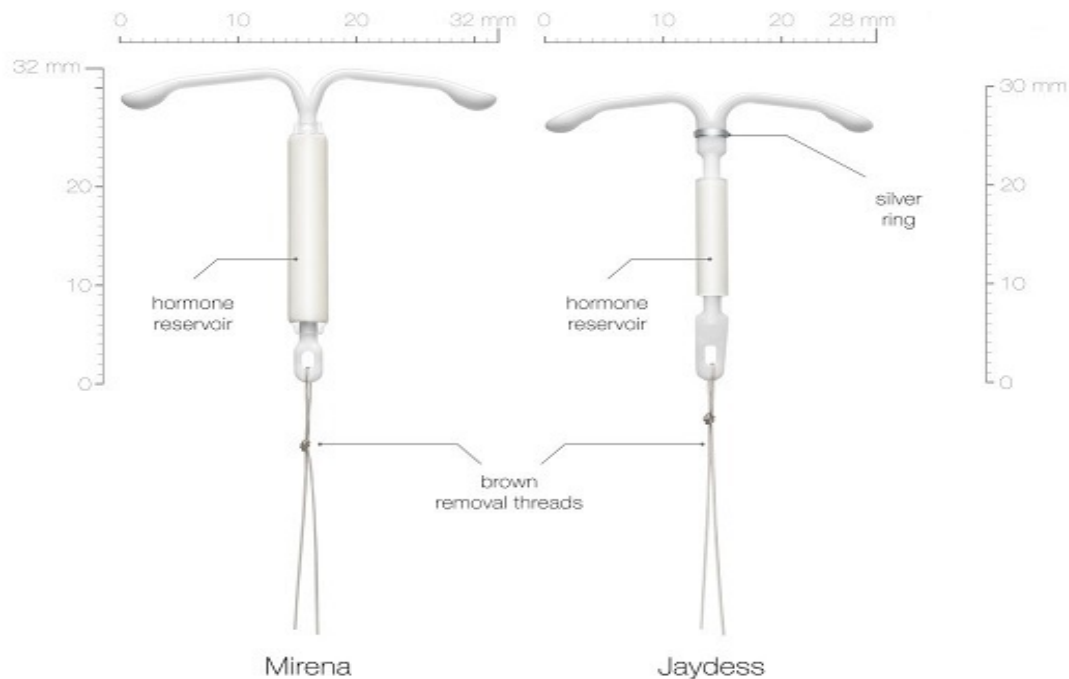


Figure 1: Physical appearance of Mirena and Jaydess

- Jaydess, 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). *Brown* 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. *Brown* coloured removal threads are attached to the loop at the end of the T-body stem.

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

d. X-ray and Ultrasound Images

- The T-body of both IUS contain barium sulphate which makes them visible in X-ray examination.
- Jaydess can be differentiated from Mirena by the silver ring that is visible in ultrasound.

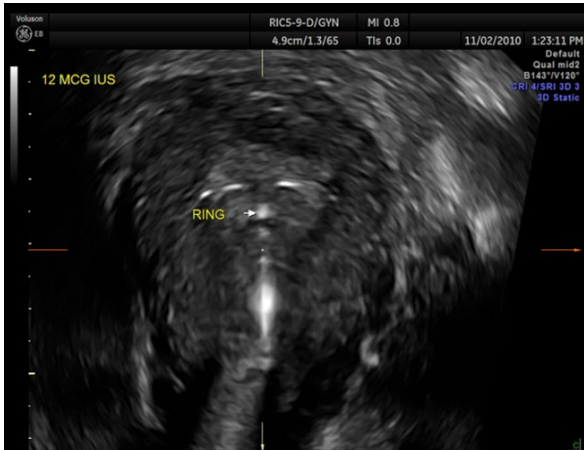


Figure 1: Jaydess – coronal plane (3 D Imaging)
 Source: Andrew Kaunitz, MD, Christine Bubier R.T.(R). RDMS, Grace Horton, RDMS und Gwyn Grabner, RDMS

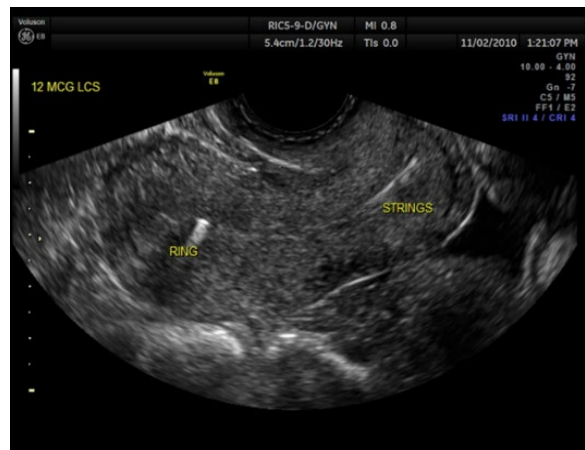


Figure 2: Jaydess – sagittal plane (2 D Imaging)
 Source: Andrew Kaunitz, MD, Christine Bubier R.T.(R). RDMS, Grace Horton, RDMS und Gwyn Grabner, RDMS

Please note, above pictures show Jaydess.

- Mirena has no silver ring



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



Figure 4: Mirena – sagittal plane (2D Imaging) Source: Dr. S. Massimo Lombardo, Munich

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

Summary

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

Jaydess can be distinguished from Mirena the visibility of the silver ring on ultrasound. Jaydess can be used for up to 3 years in the indication contraception.

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

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

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

* For the indication contraception

For differentiation of Mirena and Jaydess from LNG IUDs of other marketing authorization holders, please refer to the information provided for these products on their company website and/ or on the website of The Malta Medicines Authority.

References

- ¹ 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
- ² 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.
- ³ 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
- ⁴ Torpy JM, Burke AE, Golub RM. JAMA patient page. Ectopic pregnancy. *JAMA* 2012;308:829.
- ⁵ NHS Choices, Symptoms of Ectopic Pregnancy, 2019. Available at <https://www.nhs.uk/conditions/ectopic-pregnancy/symptoms/> (accessed 15 July 2019)
- ⁶ 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

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.

⁷ 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.

⁸ 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

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at <http://www.medicinesauthority.gov.mt/adrportal>, and sent by post or email to:

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

Or

E: pv@alfredgera.com

Prescriber guide approved by the Malta Medicines Authority May 2021. The Prescriber Guide is in line with the conditions of the marketing authorisation.