



Faculty of Sexual & Reproductive Healthcare

New Product Review from the Clinical Effectiveness Unit

Jaydess® Levonorgestrel Intrauterine System (LNG-IUS)

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Description

Jaydess® is a levonorgestrel intrauterine system (LNG-IUS) newly launched in the UK for contraception. It is a smaller, lower dose version of the Mirena® LNG-IUS.

Key Differences from Mirena LNG-IUS

- The core of the Jaydess LNG-IUS contains 13.5mg levonorgestrel, compared with 52mg levonorgestrel in the Mirena LNG-IUS
- Jaydess is licensed for 3 years, whereas Mirena is licensed for 5 years of contraceptive use
- Jaydess has a smaller frame and narrower inserter tube (table 1)
- The release rates and serum levels of levonorgestrel are lower (tables 2)
- Jaydess is only licensed for contraception (see licensed indications in table 1)
- Women using Jaydess are less likely to experience amenorrhoea
- Higher failure rates and ectopic pregnancy rates have been reported in some trials of Jaydess but numbers are currently too small to confirm a significant difference
- Jaydess contains a silver ring (table 1) which distinguishes it from other intrauterine devices on ultrasound scan or x-ray
- The safety and efficacy of Jaydess have not been studied in women aged below 18 years
- The Summary of Product Characteristics (SPC) for Jaydess states that it is not first choice for contraception in nulliparous women as clinical experience is limited

Similarities with Mirena LNG-IUS

- Other adverse events in clinical studies similar to adverse event profile of Mirena LNG-IUS
- Technique for loading and inserting Jaydess (illustrated in the SPC) is the same as for the current Mirena insertion device
- As for the Mirena LNG-IUS, the SPC for Jaydess advises insertion within seven days of the onset of menstruation or replacement at any time in the cycle
- Faculty of Sexual & Reproductive Healthcare (FSRH) recommendations for Mirena¹ would apply when inserting Jaydess at other times in the cycle, after abortion or childbirth, or when switching to Jaydess from other methods

Benefits

- In theory Jaydess may be easier to insert and result in less pain at insertion than Mirena but there have been no comparisons with the currently available Mirena product

Cost

- Jaydess NHS price £69.22 (NHS price for Mirena £88)

Background

Intrauterine contraception is available as either a copper intrauterine device (Cu-IUD) or the levonorgestrel intrauterine system (LNG-IUS). Until recently the Mirena® LNG-IUS (Bayer plc.), has been the only licensed LNG-IUS available in the UK.

Jaydess® (Bayer plc.) is an LNG-IUS which has been newly launched onto the UK market. It is designed to administer levonorgestrel into the uterine cavity at a lower daily dose than Mirena (tables 1 and 2). It is known as Skyla® in the USA where it has been licensed since 2013.² Jaydess will not replace Mirena but will instead afford women greater contraceptive choice.

Clinical studies have examined various strengths and sizes of LNG-IUS. The terminology in the literature is inconsistent as some studies describe the different LNG-IUS devices according to their LNG content, whereas others use the release rate. For consistency the LNG content is used in this review. The review evaluates the available evidence, highlighting differences and potential benefits of the LNG-IUS 13.5mg, Jaydess.

Data from phase II and III studies have been reported in three publications. Gemzell-Danielson et al. conducted a randomised phase II study of Jaydess, Mirena and an intermediate dose LNG-IUS releasing 16 µg/day (equivalent to an IUS content of 19.5mg LNG).³ Nelson et al compared two doses of LNG-IUS (Jaydess and LNG-IUS 19.5mg) in a randomised phase III study.⁴ The LNG-IUS 19.5 is not licensed or available commercially. A recent publication has reported pooled pharmacokinetic and pharmacodynamic analyses from the phase II and III studies.⁵

This review is intended to inform health professionals and is not a guidance document. FSRH guidance on intrauterine contraception is currently being updated and will be published in 2014.

Table 1 Product differentiation between Jaydess and Mirena. (Produced by Bayer Healthcare, reproduced with permission⁶)

Dimensions	Jaydess® 	Mirena® 
Insertion tube diameter	3.80mm	4.40mm
Duration of use	3 years	5 years
Dose	13.5mg	52mg
Indications	Contraception	Contraception Idiopathic menorrhagia Endometrial protection in HRT

Table 2 Levonorgestrel release rates and serum levels associated with Jaydess and Mirena IUS

Time from insertion	Release rate (µg/day)		Serum level (pg/ml)*	
	Jaydess ⁷	Mirena ⁸	Jaydess ⁷	Mirena ⁹
24 hours	14	20	-	-
60 days	10	-	-	-
1 year	6	-	162	191
2 years	-	-	-	157
3 years	5	-	59	134
4 years	N/A	12	N/A	-
5 years	N/A	10	N/A	-
6 years	N/A	-	N/A	133

* **Note:** The contraceptive effect of the LNG-IUS is predominantly a local effect, therefore systemic serum levels should not be assumed to be an indicator of efficacy or other local effects.

How effective is the LNG-IUS 13.5mg, Jaydess?

In the phase II randomised controlled trial (RCT) which compared 239 women using Jaydess (LNG-IUS 13.5mg) to 245 women using LNG-IUS 19.5mg and 254 women using Mirena (LNG-IUS 52mg), the reported Pearl Indices were 0.17 (95% CI: 0.00 - 0.93); 0.82 (CI: 0.27 - 1.92); and 0 (CI: 0 - 0.59), respectively.³

The phase III RCT including 1432 Jaydess users showed a Pearl Index of 0.41 (95% CI 0.13 - 0.96) at one year and cumulative Pearl Index after 3 years' use of 0.33 pregnancies per 100 women-years (95% CI 0.16 - 0.60). In the 1452 women using LNG-IUS 19.5mg a similar Pearl Index of 0.31 per 100-women-years (95% CI 0.15 - 0.57) was reported at 3 years.⁴ The Kaplan-Meier estimate for the cumulative failure rate of Jaydess over 3 years was 0.9%.⁴ Directly comparative figures are unavailable but the Summary of Product Characteristics for Mirena⁸ quotes a cumulative failure rate of 0.7% at 5 years, and National Institute for Health and Care Excellence (NICE) guidelines quote a failure rate for Mirena IUS as fewer than 1.0% at 5 years.¹⁰

In both phase II and III studies assessment of cervical mucus showed low Insler scores with use of all LNG-IUS doses, indicating very similar progestogenic effects on cervical mucus.⁵ A lower incidence of anovulation was observed in Jaydess users than in Mirena users but ovulation was observed in the majority of women in all three LNG-IUS groups.⁵

How do side effects and bleeding patterns compare?

Despite lower serum levels of levonorgestrel, current evidence does not suggest any clinically significant advantage in terms of side effect profile.

Jaydess trial data show a decrease in the number of bleeding or spotting days over time with all doses of LNG-IUS. There were more days with spotting only than with bleeding in all reference

periods. The main difference appears to be a lower rate of amenorrhoea in Jaydess users. In Jaydess, LNG-IUS 19.5mg and Mirena groups the proportion of subjects with amenorrhoea increased from 2.7%, 6.1% and 5.9%, respectively, in the second 90-day reference period (3-6 months after insertion) to 12.7%, 18.9% and 23.6% of subjects in the final reference period from 33 to 36 months ($p=0.12$ for Jaydess versus Mirena). While less amenorrhoea may appeal to some women it may be perceived as a disadvantage by others.

How should the LNG-IUS 13.5mg Jaydess be used?

The insertion and removal procedures for Jaydess are similar to those for Mirena. The SPC for Jaydess states that healthcare professionals should ensure that they are experienced in IUS insertions or that they have undergone training in the Jaydess insertion procedure.⁷ The FSRH advises that health professionals offering intrauterine contraception should hold the FSRH Letter of Competence or have achieved equivalent recognised competencies. Information on intrauterine device insertion training is available on the FSRH website: www.fsrh.org/

In clinical trials there was no difference in rates of non-placement of Jaydess or Mirena. Healthcare professionals reported that the placement of lower dose LNG-IUS devices was easier than placement of Mirena in both nulliparous and parous women.^{3,4} However the Mirena IUS used in the trials was different from the currently available Mirena product which contains a more ergonomic insertion system, the Evoinsertor,¹¹ similar in design to that used in Jaydess. The Mirena insertion system used in the trials was also broader (diameter 4.75mm). No studies have compared ease of insertion of the currently available Mirena product (diameter 4.4mm) with insertion of Jaydess (diameter 3.8mm).

What is the risk of ectopic pregnancy?

The absolute risk of ectopic pregnancy is reduced in women using contraception but if a pregnancy occurs during intrauterine device use the relative risk of ectopic pregnancy is increased.

The SPC for Jaydess quotes an ectopic rate of 0.11 per 100 woman-years, and warns that approximately half of the pregnancies that occur during Jaydess use are likely to be ectopic.⁷ Therefore women who become pregnant while using Jaydess are advised to seek advice to exclude ectopic pregnancy. The proportion of ectopic to intrauterine pregnancies reported in intrauterine device users may vary with the type of device and the extent to which the study population is monitored. NICE guidance states that if a woman becomes pregnant with a Mirena IUS in situ, the risk of the pregnancy being ectopic is about 1 in 20.¹⁰ However, a range of figures is reported in the literature, with one cross-sectional study reporting that approximately half of pregnancies reported in women with Mirena in situ were ectopic.¹²

Ectopic pregnancy rates in Jaydess and Mirena LNG-IUS users are difficult to compare because the number of reported pregnancies in Jaydess users has been low. There was only one ectopic pregnancy out of two Jaydess failures in phase II studies, and three ectopic pregnancies out of seven failures in phase III studies.¹³ In the study that included Mirena, the ectopic pregnancy rate was non-significantly increased in Jaydess users compared with Mirena users, but the ectopic rate was highest in women using the intermediate dose LNG-IUS 19.5mg. The phase III data also showed a non-significantly higher ectopic pregnancy rate in LNG-IUS 19.5mg group (0.22 per 100 woman-years) than in the Jaydess group (0.10 per 100 woman-years). Therefore, the data do not support a dose-response effect on ectopic pregnancy rate. Furthermore, the ectopic pregnancy rates for Jaydess are expressed as woman-years, preventing direct comparison with the rates quoted in the literature for Mirena, (1 in 1000 in 5 years¹⁰ and 0.1% per year⁸).

These limitations and the lack of a dose-response effect mean that differences in the absolute and relative risks of ectopic pregnancy between different dose LNG-IUS should be interpreted with caution until more pregnancy data are available.

What other adverse events have been reported?

In phase III studies the cumulative risk of expulsion of Jaydess was reported as 4.56% over 3 years of use.⁴ The same trial observed no reduction in bone mineral density (BMD) from baseline at either the lumbar spine or total hip over 3 years in the LNG-IUS 13.5mg group.⁴

Other trial data³ showed that significantly more ovarian cysts >3cm in diameter were observed in a group using Mirena than groups using two lower dose LNG-IUS: 22% in Mirena users; 8.6% in LNG-IUS 19.5mg users; and 5.9% in Jaydess users, ($p < 0.0001$).

Are there any restrictions on use?

The United Kingdom Medical Eligibility Criteria for Contraceptive Use (UKMEC)¹³ is an agreed set of criteria for providing contraception to men or women with a range of medical conditions. Jaydess was not available in the UK when UKMEC was last updated. However, the CEU would recommend that the UKMEC classifications for the LNG-IUS are used for Jaydess. This means that according to FSRH guidance, use of Jaydess in women under 18 years of age should not generally be restricted (UKMEC 2 from menarche to <20 years: benefits generally outweigh the risks). There are no restrictions on use of LNG-IUS in nulliparous women.

Are there any drug interactions?

Theoretically, because Jaydess and Mirena contain the same contraceptive hormone and have a similar local mechanism of action, drug interactions with Jaydess should be broadly similar to those of Mirena.

User satisfaction and pain

Satisfaction rates were high and discontinuation low across all LNG-IUS groups. Neither of the clinical trials used a validated measure of pain.^{3;4} Subjects were asked to rate pain during placement as 'none', 'mild', 'moderate' or 'severe'. The need for cervical dilatation, local anaesthesia, or pain medication was at the physician's discretion. These outcomes were recorded but it is not clear how they influenced women's perception of pain. Of the subjects in the combined Jaydess/LNG-IUS 19.5mg group 350/484 (72.3%) reported 'no pain' or 'mild pain' compared with 147/254 (57.9%) in the Mirena group ($p < 0.001$).³ There is no evidence investigating differences in pain associated with insertion of the currently available Mirena IUS and Jaydess.

Cost

The unit price for Jaydess to the NHS will be £69.22. The net price for Mirena® is £88.00.¹⁴

A US study has suggested that women switching to the LNG-IUS 13.5 mg from a short-acting method may generate cost savings, principally via a decrease in costs associated with unplanned pregnancy expenditure; and that there may also be savings in terms of contraceptive costs in the long-term.¹⁵ No cost-effectiveness comparisons were identified with Mirena or the potentially cheaper hybrid LNG-IUS products that are being introduced for treatment of heavy menstrual bleeding and that may be licensed for contraception.¹⁶

What does the LNG-IUS 13.5mg Jaydess add to the range of contraceptives already available?

The LNG-IUS 13.5mg Jaydess may appeal to women who prefer to have more regular bleeding rather than amenorrhoea. The smaller dimensions of Jaydess may be a theoretical advantage in terms of ease of fitting and less pain associated with insertion, particularly in young nulliparous women. However there is a lack of data on use in young women and there have not been any direct comparisons with the Mirena product currently in use. Therefore more robust data are required to confirm such advantages.

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