

## DTB CPD/CME\*

BNF 7.3.2.3

## ▼Jaydess IUS

In the UK, around 75% of women of reproductive age use some form of contraception.<sup>1</sup> Although combined oral contraceptives and barrier contraception are the most widely used, their effectiveness is dependent on their correct and consistent use. In contrast, long-acting reversible contraceptives provide effective and reliable methods of contraception that are not reliant upon user adherence.<sup>2</sup> ▼Jaydess (Bayer) is a new long-acting reversible levonorgestrel-releasing intra-uterine delivery system (IUS) that provides contraception for up to 3 years.<sup>3</sup> It was launched in April 2014, and is the second levonorgestrel IUS available in the UK. Here we discuss the evidence for its effectiveness and safety, and consider its place in therapy.

## Background

Long-acting reversible contraception (LARC) encompasses any method that requires administration less than once per month or once per menstrual cycle, and includes copper intra-uterine devices (IUDs), levonorgestrel IUS, progestogen-only injectable contraceptives and progestogen-only subdermal implants.<sup>2</sup>

## About Jaydess IUS

Jaydess consists of a drug core matrix mounted on a polyethylene T-frame (28mm × 30mm × 1.55mm) that also contains barium sulphate and a silver ring to aid in detection and differentiation by ultrasound and x-ray.<sup>3</sup> It has a smaller frame and narrower insertion tube compared with Mirena (Bayer), a levonorgestrel IUS launched in 1995.<sup>4,5</sup> The drug reservoir of Jaydess contains 13.5mg levonorgestrel and is designed to provide a lower daily release rate and result in lower systemic exposure to levonorgestrel than Mirena, which contains 52mg levonorgestrel and lasts for up to 5 years.<sup>5</sup> Jaydess is licensed for contraception for up to 3 years.<sup>3</sup> The Summary of Product Characteristics (SPC) states that safety and efficacy has not been studied in women aged below 18 years.<sup>3</sup>

The insertion technique for Jaydess is similar to that of Mirena and should only be performed by healthcare professionals who are experienced in IUS

insertions and/or have undergone training on the procedure.<sup>3,4</sup> Jaydess is inserted into the uterine cavity within 7 days of the onset of menstruation, and may be replaced with a new system at any time in the cycle. Jaydess can be inserted immediately after first trimester termination. It is recommended that postpartum insertions should be delayed until 6-12 weeks after delivery.<sup>3</sup>

## Clinical efficacy

The public assessment report summarising the contraceptive efficacy of Jaydess included one phase 3 trial and a supportive phase 2 trial.<sup>6,7</sup> Both were multicentre randomised open-label studies that included generally healthy nulliparous and parous women who had regular menstrual cycles and requested intra-uterine contraception. The majority of subjects were

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Caucasian, and treatment groups were comparable with regard to body weight and gynaecological history.<sup>8</sup> The primary efficacy outcome in both studies was pregnancy rate, expressed as the Pearl Index (number of pregnancies per 100 woman-years conceived during treatment [see Box]). Secondary outcomes included failure rates, bleeding patterns, and ease and pain of placement.

### Box: Guidance on assessing contraceptive efficacy<sup>9</sup>

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guidance on the clinical investigation of steroid contraceptives states that non-comparative studies are acceptable but a sufficient number of cycles should be studied to obtain the desired precision of the estimate of contraceptive efficacy. Key studies should be large enough to give the overall Pearl Index with a two-sided 95% confidence interval (CI) such that the difference between the upper limit of the CI and the point estimate does not exceed 1.

The phase 3 study randomised 2,885 women aged 18–35 years to 3 years treatment with one of two levonorgestrel-releasing IUS: 13.5mg total content (Jaydess) or 19.5mg total content (not licensed in the UK).<sup>6</sup> The devices had the same size T-frame (28mm x 30mm) and were positioned using identical 3.8mm placement tubes. Successful placement was achieved in 1,426 out of 1,432 women in the Jaydess group.<sup>6</sup> The first insertion attempt was successful in 96% of instances, and the second attempt in 94%.<sup>10</sup> Study investigators rated the insertion procedure as 'easy' in 90% of women. During insertion of the IUS, 21% of women experienced no pain and 44% mild pain. Moderate pain was experienced by 27% of women and severe pain by 8%, with a trend towards less pain in parous women.

In the Jaydess group, just over 57% of women completed the planned treatment duration of 3 years. The unadjusted 1-year Pearl Index was 0.41 (95% CI 0.13 to 0.96), and after 3 years was 0.33 (95% CI 0.16 to 0.60). The Kaplan-Meier estimate for the cumulative failure rate was 0.4% over 1 year and 0.9% at 3 years. The failure rate also included pregnancies occurring after undetected expulsions and perforations.<sup>3</sup> There was no significant difference in the pregnancy rate with respect to parity.

The mean number of bleeding and spotting days decreased over time, with more spotting-only days than bleeding days reported in all 90-day reference periods over 3 years. Of the 74% of women in the Jaydess group who completed a user satisfaction questionnaire, 95% rated themselves as 'very satisfied' or 'somewhat satisfied' with study treatment, and 77% were 'very satisfied' or 'somewhat satisfied' with their bleeding patterns.

The main objective of the phase 2 trial was to select an appropriate and effective dose for the new levonorgestrel IUS for a phase 3 study.<sup>7</sup> A total of 742 women aged 21–40 years were randomised to treatment with one of three formulations of levonorgestrel IUS: 13.5mg total content (Jaydess; T-frame size 28mm x 28mm), 19.5mg total content (T-frame size 28mm x 28mm) or 52mg total content (Mirena; T-frame size 32mm x 32mm). The primary outcome was the pregnancy rate expressed as the Pearl Index. However, the study was not powered to demonstrate non-inferiority against Mirena. The three treatment groups were well balanced, except for a higher rate of current smokers in the Mirena group.<sup>7</sup> Approximately 70% of women in the three groups completed the 3-year study. The 3-year Pearl Index was 0.17 (95% CI 0.00 to 0.93) in the Jaydess group and 0.00 (95% CI 0.00 to 0.59) in the Mirena group. The Kaplan-Meier estimates for the cumulative failure rate over 3 years were 0.5% and 0.0%, respectively. The mean number of bleeding and spotting days decreased similarly over time in each of the treatment groups. Investigators rated placement as 'easy' for 94% of subjects in the combined 13.5mg and 19.5mg levonorgestrel groups compared with 86% in the Mirena group ( $p < 0.001$ ). Subjects rated placement of Jaydess less painful compared with Mirena ( $p < 0.001$ ).

## Safety

Safety assessments were based on a pooled analysis of data across both studies, and for each individual study.<sup>6–8,11</sup> The pooled data on Jaydess cover more than 40,000 28-day cycles of exposure of which around one third were in nulliparous women.<sup>11</sup>

In general, the adverse event profile of Jaydess is consistent with that expected for a levonorgestrel intra-uterine contraceptive and did not raise any new safety concerns.<sup>11</sup> Overall, there were no clinically relevant differences between treatment groups in the rate and severity of adverse events.<sup>8</sup> The safety profile varied slightly by parity, with more adverse events reported in nulliparous women. The most common adverse events associated with study discontinuation were menstrual bleeding disorders, IUS expulsion, acne and pelvic pain.<sup>11</sup> Other treatment-emergent adverse event were similar to those that occur with the use of Mirena and included ovarian cysts, dysmenorrhoea, headache, pelvic pain and breast discomfort.<sup>3,4</sup> The majority of women had irregular bleeding and spotting in the first few months after insertion of Jaydess. In the Jaydess and Mirena groups, the proportion of women with amenorrhoea at 33–36 months was 13% and 24%, respectively ( $p = 0.012$ ).<sup>7</sup>

Serious adverse events occurred in less than 5% of women in the Jaydess group; the most common that were considered to be related to the study drug included ectopic pregnancies, ovarian cysts, pelvic inflammatory disease (PID), spontaneous abortion and abdominal pain.<sup>11</sup> A total of four ectopic pregnancies occurred during treatment with Jaydess (pooled data), equating to an absolute ectopic pregnancy rate of 0.2% over 3 years' use. The overall risk of ectopic pregnancy was 0.11 per 100-women years, which is lower than in women not using any contraception (0.3–0.5).<sup>2,12</sup> The SPC states that the absolute rate of ectopic pregnancy in Mirena users is 0.1% per year.<sup>4</sup> The cumulative risk of expulsion was low (3.7%) and in the range reported for other IUS and IUDs.<sup>8</sup> The overall rate of PID was 0.4% in the Jaydess group, all of which occurred in parous women.<sup>11</sup> There was no evidence of a delay in the return of fertility following removal or expulsion of Jaydess.

## Strengths and limitations of the evidence

The two studies were well designed and the populations used were appropriate for the evaluation of the contraceptive efficacy and safety. Although only the phase 2 study included subjects from the UK, a significant proportion of women in the phase 3 study were from Europe. The primary efficacy analysis in the phase 3 study was based on all randomised subjects who had at least one IUS insertion attempt, and cycles in which other 'back-up' contraception was used were appropriately excluded. The study also included a reasonably high proportion (39%) of nulliparous women, which should be sufficient to allow evaluation of the safety and efficacy in this population.

It was not possible to blind investigators to which IUS was being inserted because of their differing dimensions and the size of the drug reservoir. The Mirena inserter was different to the product currently available in the UK, which uses a more ergonomic insertion system. The evaluations of ease and pain of insertion were subjective, and the need for cervical dilation, local anaesthesia or analgesics was at the clinicians' discretion, which may limit the applicability of these results. In the phase 3 study, almost one third of women did not complete the user satisfaction questionnaire undertaken at the final study visit, and women who discontinued before the questionnaire was introduced were not included. As treatment allocation was disclosed to subjects at 30 months in this study, the introduction of bias regarding questionnaire responses cannot be excluded.

There are no published phase 3 studies directly comparing Jaydess with other methods of contraception. However, a study comparing Jaydess with Yasmin has been completed and a comparison with Nexplanon is currently underway.<sup>13,14</sup> The European Medicines Agency (EMA) has requested a surveillance study that will enrol 38,000 women in five European countries

to investigate whether Jaydess is associated with an increased risk of unintended pregnancy and other events (e.g. contraceptive failure, ectopic pregnancy, uterine perforation and PID) compared with Mirena and copper IUDs.<sup>15</sup> The estimated primary completion date is June 2018.

## Contraindications, special warnings and precautions for use

The contraindications, special warnings and precautions for Jaydess are broadly in line with those for Mirena.<sup>3,4</sup> Contraindications to use include pregnancy, acute or recurrent PID, acute cervicitis or vaginitis, postpartum endometritis or infected abortion, abnormal vaginal bleeding, uterine or cervical malignancy, progestogen-sensitive tumours, and congenital or acquired uterine anomalies.

Jaydess is not recommended as the first choice in nulliparous women as clinical evidence in this group is limited. The company recommends that women considering the levonorgestrel IUS should be counselled on the signs, symptoms and risks of ectopic pregnancy. As an ectopic pregnancy may affect future fertility, the company advises that the benefits and risks of using Jaydess should be carefully evaluated, especially in nulliparous women.

Jaydess should be used with caution after specialist advice, or removal should be considered in women with existing or new severe headache, migraine, jaundice, severe arterial disease such as stroke or myocardial infarction, or marked increase in blood pressure. Although low-dose levonorgestrel may affect glucose tolerance, it is not usually necessary to alter the therapeutic regimen in women with diabetes.<sup>3</sup>

## Cost

Comparison of the relative costs of LARC methods are complicated by the differing durations of action and the variation in administration and service costs associated with their provision (see Table).

There are insufficient data to allow evaluation of the cost-effectiveness of Jaydess compared with other methods of LARC. The National Institute for Health and Care Excellence (NICE) considers all currently available LARC methods to be more cost-effective than the combined oral contraceptive pill even for 1 year of use.<sup>2</sup> The IUD, IUS and implants are more cost-effective than the injectable contraceptives.

## What do national guidelines say?

In September 2014, NICE published updated guidance on the use of LARC.<sup>2</sup> The guideline aims to promote wider contraceptive choice by recommending that women requiring contraception should be given information about, and offered a choice of, all methods. Women considering LARC should receive detailed verbal and written information to enable them to choose a method and use it effectively. The guideline also highlighted the role of LARC methods in the reduction of unintended pregnancy, especially unintended teenage pregnancies. All LARC methods were presented as highly reliable and cost-effective for the NHS. Jaydess was not included in the guideline as it was not licensed for use in the UK when the review was started. However, a recent evidence summary published by NICE suggests that Jaydess is an alternative to other LARC methods.<sup>16</sup>

The Faculty of Sexual and Reproductive Healthcare summary on Jaydess suggests that it may appeal to women who prefer to have more regular bleeding rather than amenorrhoea, and that its smaller dimensions may be a theoretical advantage in terms of ease of fitting and less pain associated with insertion. The authors note that there is a lack of data on use in young women and there have not been any direct comparisons with the version of Mirena currently available.<sup>5</sup>

The Scottish Medicines Consortium is currently appraising Jaydess and is expected to publish its advice in April 2015.<sup>17</sup> The All Wales Medicines Strategy Group also has a forthcoming appraisal, but the expected publication date is not yet available.<sup>18</sup>

**Table: Cost of long-acting reversible contraception methods (excluding administration costs)**

Product	Strength	Duration of action	Cost	Cost per year
▼Jaydess IUS	13.5mg	3 years	£69.22	£23.07
Mirena IUS	52mg	5 years	£88.00	£17.60
Copper IUD	A range of devices are available	5 or 10 years	£7.95–£27.11	£0.90–£5.42
Etonogestrel implant (Nexplanon)	68mg subdermal implant	3 years	£79.46	£26.49
Medroxyprogesterone acetate (Depo-Provera)	150mg/mL intramuscular injection	12 weeks (+5 days)	£6.01	£30.05
Medroxyprogesterone acetate (Sayana Press)	104mg/0.65 mL subcutaneous injection	13 weeks (±7 days)	£6.90	£27.60

Costs based on prices in *Chemist and Druggist* and the *Drug Tariff*.

## Conclusion

▼Jaydess is a new levonorgestrel-releasing intra-uterine system (IUS) licensed for the prevention of pregnancy for up to 3 years. Evidence from one study suggests that Jaydess has a failure rate of approximately 0.4% at 1 year, and a cumulative failure rate of approximately 0.9% over 3 years. This is comparable to the failure rates reported with the correct and consistent use of other established methods of LARC, including Mirena. In one study, the proportion of women with amenorrhoea at 33–36 months was lower with Jaydess than with Mirena. The overall safety profile for Jaydess is consistent with that expected for a levonorgestrel-containing intra-uterine contraceptive. Despite the lower levonorgestrel release rate it does not appear to confer any significant advantages in terms of adverse effects over Mirena. However, there have been no direct comparisons between the versions of the two products currently available.

Whilst there may be a theoretical advantage of Jaydess's smaller frame, narrower insertion tube and lower levonorgestrel release rate compared with Mirena, this needs to be balanced by its shorter lifespan. Furthermore, Jaydess is not currently recommended as the first choice in nulliparous women as clinical evidence in this group is limited. In the absence of any major advantage in terms of efficacy, safety, user acceptability or cost there seems little reason to use Jaydess in preference to Mirena.

[R=randomised controlled trial; M=meta-analysis]

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