

## Faculty of Sexual and Reproductive Healthcare

### New Product Review: Kyleena 19.5 mg intrauterine delivery system

#### 29 January 2018 (Amended 22 March 2019)

#### Description

Kyleena<sup>®</sup> (Bayer plc) is a levonorgestrel (LNG) intrauterine system (IUS) that is licensed for contraceptive use for 5 years. Kyleena is not licensed for management of heavy menstrual bleeding and is not licensed to provide endometrial protection as part of hormonal replacement therapy (Table 1).

Kyleena contains 19.5mg LNG in a reservoir mounted on a T-shaped frame. LNG content is lower than that of Mirena<sup>®</sup> and Levosert<sup>®</sup> (both 52mg LNG) and higher than Jaydess<sup>®</sup> (13.5mg). The T-frame dimensions (28x30mm) are identical to those of Jaydess and the introducer is also the same design and dimensions as for Jaydess (3.8mm) (Table 1).

This review is intended to inform health professionals and is not a guidance document. For further information about medical eligibility, health benefits, side effects and health risks associated with use of LNG-IUS, please refer to FSRH guidance on intrauterine contraception<sup>1</sup> available on the FSRH website: <https://www.fsrh.org/standards-and-guidance/documents/ceuguidanceintrauterinecontraception/> Note that UKMEC recommendations for the LNG-IUS apply to Kyleena.<sup>2</sup>

#### Differentiation between LNG-IUS products available in the UK

The key differences in product characteristics between the LNG-IUS currently available in the UK are summarised in Table 1 below.

**Table 1: Product characteristics of Kyleena, Mirena, Levosert and Jaydess.**

Type of LNG-IUS	Kyleena <sup>3</sup>	Mirena <sup>4</sup>	Levosert <sup>5</sup>	Jaydess <sup>6</sup>
Total LNG content (mg)	19.5	52	52	13.5
LNG release rate (mcg/24h)				
Initial	17.5	20	19.5	14
Final	7.4 (after 5 year)	10 (after 5 years)	9.8 (after 5 years)	5 (after 3 years)
Average	9 (over 5 years)	14 (over 5 years)	14.7 (over 5 years)	6 (over 3 years)
Frame size (W x H, mm)	28 x 30	32 x 32	32 x 32	28 x 30
Inserter	One handed EvoInserter™	One handed EvoInserter™	Two-handed inserter	One handed EvoInserter™
Insertion tube diameter (mm)	3.8	4.4	4.8	3.8
Silver ring for improved visibility on USS?	Yes	No	No	Yes
Colour of threads	Blue	Brown	Blue	Brown
Licensed duration of use for contraception (years)	5	5	5	3

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Type of LNG-IUS	Kyleena	Mirena	Levosert	Jaydess
Licensed for endometrial protection?	No	Yes	No	No
Licensed for heavy menstrual bleeding?	No	Yes	Yes	No
Minimum uterine cavity length (cm)	Not indicated in SPC	Not indicated in SPC	5.5 cm	Not indicated in SPC
Unit cost (£)	76	88	66	69.22
Cost per year over period of licensed use (£/year)	15.2	17.6	13.2	23.07

LNG-IUS: Levonogestrel-releasing intrauterine system; USS: Ultrasound scan

### Data source

Limited data from phase II and III studies are reported in three publications comparing Kyleena with Jaydess and Mirena. No published study compares Kyleena with Levosert. Terminology in the literature is inconsistent; some studies describe the different LNG-IUS devices according to their LNG content, some according to their in vitro release rates and others use the in vivo release rate. For consistency, the product names are used in this review.

Gemzell-Danielson *et al.* (2012) reported on a multicentre, open-label, randomised three-arm phase II study, which included a total of 738 women successfully fitted with Kyleena ( $n=245$ ), Jaydess ( $n=239$ ) or Mirena ( $n=254$ ).<sup>7</sup> The study period was 3 years. This study was not powered to determine whether there was a significant difference in contraceptive effectiveness between the devices.

A large multicentre, open-label, randomised two-arm phase III study which included a total of 2,884 women. Nelson *et al.* (2013) compared women fitted with Kyleena ( $n=1,452$ ) or Jaydess (1,432) over a study period of 3 years. 870 women using Kyleena and 819 using Jaydess completed the 3 year study.<sup>8</sup> 707 women in the trial who were using Kyleena then entered an optional 2 year trial extension period and the resulting 5 years of data for Kyleena were reported by Gemzell-Danielson *et al.* (2017).<sup>9</sup>

### How does contraceptive effectiveness of Kyleena compare to other LNG-IUS?

The phase III trial<sup>9</sup> reported an unadjusted Pearl Index of 0.29 (95% confidence interval [CI] 0.16-0.50) for Kyleena over the 5-year duration of use. The reported cumulative failure rate at 5 years was 1.45% (0.18% at 1 year, 0.97% at 3 years). A total of 5 intrauterine and 8 ectopic pregnancies were observed.

Comparing Kyleena and Jaydess over 3 years of use, the study reported a 3 year Pearl Index of 0.31 for Kyleena and 0.33 for Jaydess and a cumulative failure rate at 3 years of 1% for Kyleena and 0.9% for Jaydess.<sup>8</sup>

The phase III study<sup>9</sup> did not include Mirena or Levosert. The Summary of Product Characteristics (SPC) for Mirena<sup>4</sup> notes a Pearl Index of 0.2 for the first year of use and a cumulative failure rate at 5 years of 0.7%. The SPC for Levosert<sup>5</sup> notes a contraceptive failure rate of approximately 0.19% (95% CI: 0.05% - 0.75%) per year.

**The contraceptive effectiveness of Kyleena appears comparable to other LNG-IUS devices at 1 and 3 years of use. No study has directly compared contraceptive effectiveness of Kyleena and Mirena over 5 years of use. However, the reported pregnancy rates are low throughout five years of use of Kyleena.**

### **How do bleeding patterns compare?**

#### *Bleeding/spotting days*

Both the phase II and phase III studies report that the mean number of bleeding spotting days decrease over time with Kyleena and Jaydess<sup>7,8</sup> as is observed with Mirena.<sup>7</sup>

The phase II and III study authors' graphical representation of the data suggests that the mean number of bleeding days over the course of 3 years is lower with Mirena than with Kyleena<sup>7</sup> and lower with Kyleena than with Jaydess.<sup>7,8</sup> However statistical significance is not reported. This limited evidence suggests the possibility that higher doses of LNG in the LNG-IUS could be associated with fewer bleeding/spotting days.

#### *Amenorrhoea*

The phase II trial<sup>7</sup> reported that, at 3 years, 18.9% of women using Kyleena were amenorrhoeic, compared with 23.6% using Mirena (difference not statistically significant) and 12.7% using Jaydess. In the phase III trial<sup>9</sup> the incidence of amenorrhoea with Kyleena was 12.7% at 1 year and 22.6% at 5 years.

### **How do side effects and adverse events compare?**

Commonly-reported side effects of Kyleena are similar to those with Mirena<sup>7</sup> and Jaydess<sup>7,8</sup> and include acne, pelvic pain, breast discomfort and weight gain. The limited data available demonstrate very few significant differences between the different devices in terms of side effects.

The phase III study<sup>8</sup> reported that weight gain was significantly greater with Kyleena (0.6kg at 1 year and 1.1kg at 3 years) than with Jaydess (0.2kg at 1 year and 0.5kg at 3 years),  $p < 0.03$ . Among women who continued into the phase III trial extension, mean weight gain was 2.2kg. The authors noted that this is similar to the weight gain observed over time in the general population.

### ***Ectopic pregnancy***

The 5 year phase III study<sup>9</sup> reported a Pearl Index for ectopic pregnancy with Kyleena of 0.18 over 5 years. This compares with an ectopic pregnancy rate of 0.02 per 100 woman years reported for the 52mg LNG-IUS and 0.08 per 100 woman years for the copper intrauterine device (Cu-IUD) in the EURAS-IUD study, a large observational study with 61 448 women enrolled from six European countries between 2006 and 2012.<sup>10</sup> For Jaydess, the 3 year phase III study<sup>8</sup> reported an ectopic pregnancy rate of 0.1 per 100 woman years. Data are limited and further research is required to clarify the ectopic pregnancy risk with Kyleena relative to that with other LNG-IUS.

While the absolute risk of ectopic pregnancy is not increased by use of IUC, should a pregnancy occur with an IUC *in situ* then the likelihood of it being ectopic is greater than if a pregnancy were to occur without an IUC *in situ*. Women should be informed that if pregnancy occurs with an IUC *in situ*, there is an increased risk of ectopic pregnancy and therefore the location of the pregnancy should be confirmed by ultrasound as soon as possible.

## **Expulsion**

In the phase III trial,<sup>8</sup> the cumulative risk of complete or partial expulsion over 3 years was 3.58% for Kyleena and 4.56% for Jaydess. FSRH guidance reports that approximately 1 in 20 (5%) of intrauterine contraceptives are expelled.<sup>1</sup>

## **Ease of insertion and insertion-related pain**

It has been suggested that a narrower introducer and a smaller device could be more suitable for women with a narrower cervical canal and/or smaller uterine cavity (such as nulliparous women or young women).

It should be noted that in some studies the Kyleena/Jaydess devices that were used were of slightly different dimensions and that in some studies the Mirena used had a slightly different introducer diameter. Specifically, in the phase II trial<sup>7</sup> Kyleena and Jaydess that were used had a 28x28mm frame; whereas in the phase III studies,<sup>8,9</sup> the frame measured 28x30mm (the same as current devices). The Mirena used in the phase II trial<sup>7</sup> had an insertion tube of 4.75mm diameter, whereas the currently used Mirena Evolnserter has a narrower diameter (4.4mm). Whether these small differences affect the applicability of the data on insertion and insertion related pain is unknown.

In the phase II study, 99.5% of women had an LNG-IUS inserted successfully.<sup>7</sup> Placement of Kyleena and Jaydess was rated by the clinician as “easy” in 94%, compared to 86.2% for Mirena. The difference was significant ( $p < 0.001$ ). Women rated insertion of Kyleena and Jaydess as significantly less painful than insertion of Mirena; 72.3% of women in the Kyleena/ Jaydess group reported either ‘no pain’ or ‘mild pain’ during placement compared with 57.9% of women in the Mirena group ( $p < 0.001$ ).

The phase III study<sup>8</sup> reported 96% successful placement of Kyleena/Jaydess at the first attempt and 99.5% after 2 attempts. Investigators rated placement of Kyleena/Jaydess as ‘easy’ in 90% of women and ‘very difficult’ in 1% of women. 19.5% of women in this study rated pain at insertion of Kyleena/Jaydess as ‘none’, almost half (45.5%) rated it as ‘mild’, 27.4% rated ‘moderate’ and 8% of women rated insertion pain as ‘severe’.

## **How does the cost compare?**

At the current unit price of £76 and licensed for 5 years of contraceptive use, Kyleena has a higher contraceptive cost per year over full duration of licensed use than Levosert, but lower than Mirena and Jaydess.

## **Conclusion**

- ▶ Kyleena provides an additional highly effective option for long-acting reversible contraception that is licensed for 5 years of use.
- ▶ Systemic release of LNG is lower than with the 52mg LNG-IUS.
- ▶ The contraceptive effectiveness, side effect and adverse event profile of Kyleena is similar to that of other LNG-IUS devices.
- ▶ The number of bleeding/spotting days with Kyleena reduces over time.
- ▶ The mean number of bleeding/spotting days with Kyleena is possibly more than with a LNG-IUS releasing a higher LNG dose.
- ▶ The rates of amenorrhoea with Kyleena **may possibly** be less than compared to LNG-IUS releasing a higher dose of LNG.

- ▶ The narrower insertion tube and smaller frame may make Kyleena an appropriate option if a woman has a narrow cervical canal or shorter uterine cavity but prefers a 5 year LNG-IUS.
- ▶ Insertion of Kyleena and Jaydess has been reported to be significantly easier and associated with significantly less pain than insertion of Mirena.

## References

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