EFFICACY AND BLEEDING PROFILE CONSIDERATIONS FOR KYLEENA AND MIRENA

Overview of Kyleena® and Mirena® intrauterine devices (IUDs)

- Contraceptive efficacy and safety
- Bleeding profiles
- A 3-year, phase II analysis

Kyleena® (levonorgestrel-releasing intrauterine system) 19.5 mg

Mirena® (levonorgestrel-releasing intrauterine system) 52 mg

Please see Important Safety Information throughout, and click for accompanying full Prescribing Information for Kyleena (levonorgestrel-releasing intrauterine system) 19.5 mg and Mirena (levonorgestrel-releasing intrauterine system) 52 mg.

Kyleena®
(levonorgestrel-releasing intrauterine system) 19.5 mg

HIGH CONTRACEPTIVE EFFICACY MAINTAINED OVER 5 YEARS[1]

99.8%
EFFICACY AT YEAR 1

>99%
EFFICACY FOR EACH YEAR OF USE

98.6%
CUMULATIVE EFFICACY OVER 5 YEARS

KYLEENA IS THE LOWEST DOSE 5-YEAR IUD[1]

The efficacy of Kyleena over 5 years was studied in 1452 parous and nulliparous women aged 18 to 35 years.[1]

Year 1: Pearl Index of 0.16; 95% upper CL of 0.58; cumulative 5-year pregnancy rate, based on 13 pregnancies, estimated by the Kaplan-Meier method was 1.45%; 95% upper CL of 2.53%.[1]

CL=confidence limit; IUD=intrauterine device.

INDICATION FOR KYLEENA

Kyleena® (levonorgestrel-releasing intrauterine system) 19.5 mg is indicated for the prevention of pregnancy for up to 5 years. Replace the system after 5 years if continued use is desired .

INDICATIONS FOR MIRENA

Mirena® (levonorgestrel-releasing intrauterine system) 52 mg is indicated for prevention of pregnancy for up to 7 years; replace after the end of the seventh year. Mirena is indicated for the treatment of heavy menstrual bleeding for up to 5 years in women who choose to use intrauterine contraception as their method of contraception; replace after the end of the fifth year if continued treatment of heavy menstrual bleeding is needed.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA AND MIRENA

Who is not appropriate for Kyleena and Mirena

Use of Kyleena or Mirena is contraindicated in women with: known or suspected pregnancy and cannot be used for post-coital contraception; congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity; known or suspected breast cancer or other progestin-sensitive cancer, now or in the past; known or suspected uterine or cervical malignancy; liver disease, including tumors; untreated acute cervicitis or vaginitis, including lower genital tract infections (eg, bacterial vaginosis) until infection is controlled; postpartum endometritis or infected abortion in the past 3 months; unexplained uterine bleeding; current IUD; acute pelvic inflammatory disease (PID) or history of PID (except with later intrauterine pregnancy); conditions increasing susceptibility to pelvic infection; or hypersensitivity to any component of Kyleena or Mirena.

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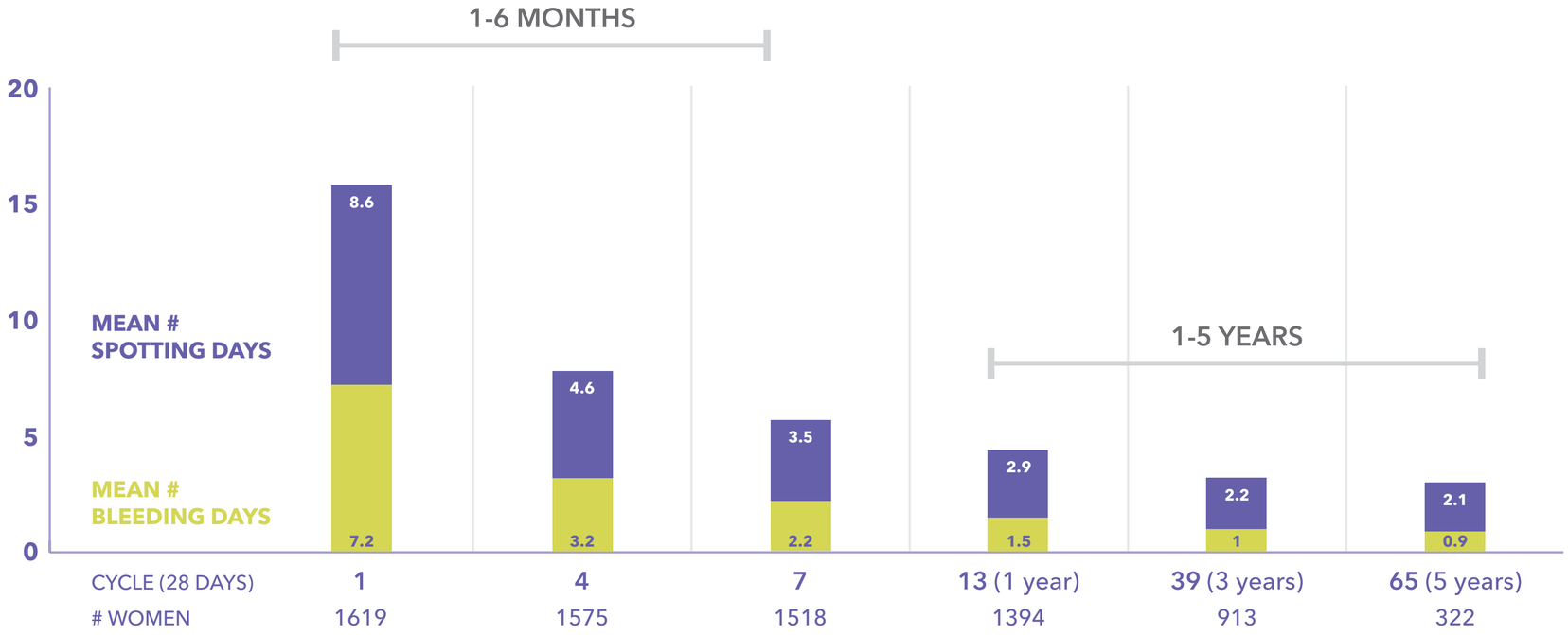
MEAN NUMBER OF BLEEDING AND SPOTTING DAYS OVER THE COURSE OF 5 YEARS[1]



- In the first 3 to 6 months of using Kyleena, patients may find that their number of bleeding and spotting days is higher and their bleeding patterns are irregular
- After 6 months, the number of bleeding and spotting days continued to decline for most women using Kyleena

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Kyleena®
(levonorgestrel-releasing intrauterine system) 19.5 mg

SOME PATIENTS EXPERIENCED AMENORRHEA AND INFREQUENT BLEEDING OVER 5 YEARS[1]

BLEEDING PATTERNS (BY 90-DAY REFERENCE PERIODS)[1]

KYLEENA	First 90 days N=1566	End of year 1 N=1371	**End of year 5 N=530**
Amenorrhea*	<1%	12%	**23%**
Infrequent bleeding†	10%	26%	**26%**
Frequent bleeding‡	25%	4%	**2%**
Prolonged bleeding§	57%	6%	**1%**
Irregular bleeding‖	43%	17%	**9%**

*Defined as subjects with no bleeding/spotting throughout the 90-day reference period.[1]
†Defined as subjects with 1 or 2 bleeding/spotting episodes in the 90-day reference period.[1]
‡Defined as subjects with more than 5 bleeding/spotting episodes in the 90-day reference period.[1]
§Defined as subjects with bleeding/spotting episodes lasting more than 14 days in the 90-day reference period. Subjects with prolonged bleeding may also be included in one of the other categories (excluding amenorrhea).[1]
‖Defined as subjects with 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 or more days.[1]

CYCLES BECOME MORE CONSISTENT OVER TIME[1]

Minimal fluctuations in bleeding and spotting after first 6 months

- Bleeding: Mean number of days overall did not fluctuate more than 1.3 days per 28-day cycle
- Spotting: Mean number of days overall did not fluctuate more than 1.4 days per 28-day cycle

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Mirena® (levonorgestrel-releasing intrauterine system) 52 mg

RELIABLE PREGNANCY PROTECTION FOR UP TO 7 YEARS[2,3]

>99.8%

CONTRACEPTIVE EFFICACY AT YEAR 1

>99.3%

CUMULATIVE EFFICACY OVER 5 YEARS

The efficacy of Mirena over 5 years was studied in 1169 women aged 18 to 35 years.[2]

12-month pregnancy rates were ≤0.2% and cumulative 5-year pregnancy rate was approximately 0.7%.[2]

99.6%

CONTRACEPTIVE EFFICACY AT YEAR 7

Women who have used Mirena for more than 5 years showed a consistent adverse reaction profile in Year 7.[2]

Percent of users experienced the following by the end of Year 7:

- Amenorrhea: 28%
- Infrequent bleeding: 26%
- Frequent bleeding: 8%
- Irregular bleeding: 12%
- Prolonged bleeding: 2%
- Weight Gain: 6% (it is unknown if the weight gain was caused by Mirena)

The contraceptive efficacy of Mirena during extended use beyond 5 years was studied in the Mirena Extension Trial, a multi-center, open-label, uncontrolled study in the US enrolling 362 women aged 18 to 35 years who had been using Mirena for not less than 4.5 years and not more than 5 years at enrollment.[2]

The PI for the 6th year of use based on the 1 pregnancy that occurred during Year 6 was 0.35 with a 95% upper confidence limit of 1.95.[2]

The PI for the 7th year of use based on the 1 pregnancy that occurred during Year 7 was 0.45 with a 95% upper confidence limit of 2.49.[2]

The cumulative 2-year pregnancy rate for Years 6 and 7 was estimated by the Kaplan-Meier method. Based on 2 pregnancies (1 in Year 6 and 1 in Year 7), the cumulative pregnancy rate at the end of the 2-year period of extended use (Years 6 and 7) was 0.71% with a 95% upper confidence limit of 2.84%.[2]

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA AND MIRENA (CONTINUED)

Clinical considerations for use and removal of Kyleena and Mirena

Use Kyleena or Mirena with caution after careful assessment in patients with coagulopathy or taking anticoagulants; migraine, focal migraine with asymmetrical visual loss, or other symptoms indicating transient cerebral ischemia; exceptionally severe headache; marked increase of blood pressure; or severe arterial disease such as stroke or myocardial infarction. Consider removing the intrauterine system if these or the following arise during use: uterine or cervical malignancy or jaundice. If the threads are not visible or are significantly shortened they may have broken or retracted into the cervical canal or uterus. If Kyleena or Mirena is displaced (e.g., expelled or perforated the uterus), remove it. Kyleena can be safely scanned with MRI only under specific conditions.

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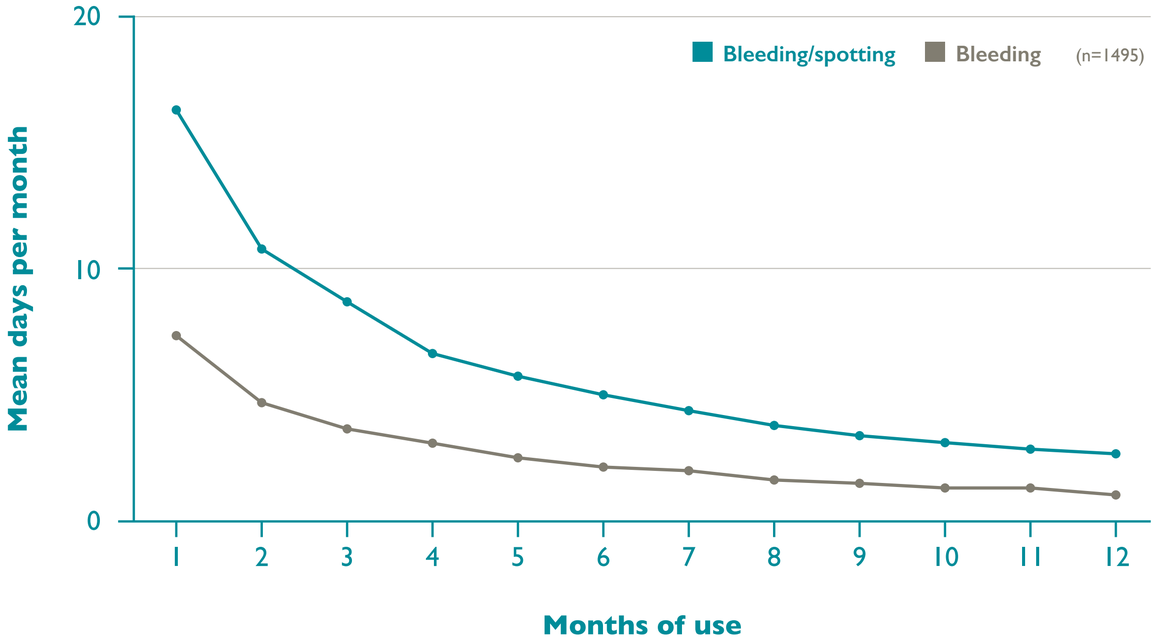
EFFECT OF MIRENA ON BLEEDING AND SPOTTING[1,2,4]

Open, randomized, multicenter study (N=2758) comparing Mirena with a copper-releasing IUD during 5 years of contraceptive use.[4]



- Spotting and irregular or heavy bleeding may occur during the first 3 to 6 months. Periods may become shorter and/or lighter thereafter. Cycles may remain irregular, become infrequent, or even cease. Consider pregnancy if menstruation does not occur within 6 weeks of the onset of previous menstruation[2]
- Because irregular bleeding/spotting is common during the first months of Mirena use, exclude endometrial pathology (polyps or cancer) prior to the insertion of Mirena in women with persistent or uncharacteristic bleeding. If a significant change in bleeding develops during prolonged use, take appropriate diagnostic measures to rule out endometrial pathology[1]
- Amenorrhea develops in approximately 20% of Mirena users by 1 year. The possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are generally not necessary in amenorrheic women unless indicated, for example, by other signs of pregnancy or by pelvic pain[2]

IUD=intrauterine device.

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Mirena® (levonorgestrel-releasing intrauterine system) 52 mg

THE FIRST AND ONLY IUD APPROVED FOR HEAVY MENSTRUAL BLEEDING (HMB) FOR UP TO 5 YEARS, FOR PATIENTS WHO CHOOSE AN IUD FOR CONTRACEPTION[2]

MIRENA SIGNIFICANTLY REDUCES BLEEDING VOLUME FOR PATIENTS WITH HMB[2]*

85%
OF WOMEN USING MIRENA EXPERIENCE TREATMENT SUCCESS

- Treatment success defined as end-of-study MBL <80 mL and a ≥50% decrease in MBL from baseline to end of study

>95%
DECREASE IN MEDIAN MENSTRUAL BLOOD LOSS (MBL) AT 6 MONTHS

- In most women with HMB, the number of bleeding and spotting days may also increase during the initial months of therapy but usually decreases with continued use; the volume of blood loss per cycle progressively becomes reduced[2]

*The safety and efficacy of Mirena in the treatment of HMB (≥80 mL MBL) were studied in a randomized, open-label, parallel-group, active-control trial comparing Mirena (n=79) to oral hormonal therapy with MPA (n=81), over 6 cycles. Women with organic or systemic conditions that can cause heavy uterine bleeding (except for small fibroids—total volume ≤5 mL) were excluded from the study.[2]

MPA=medroxyprogesterone acetate.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA AND MIRENA (CONTINUED)

Pregnancy related risks with Kyleena and Mirena

If pregnancy should occur with Kyleena or Mirena in place, remove the intrauterine system because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Advise her of isolated reports of virilization of the female fetus following local exposure to LNG during pregnancy with an LNG IUS in place. Removal or manipulation may result in pregnancy loss. Evaluate women for ectopic pregnancy because the likelihood of a pregnancy being ectopic is increased with Kyleena or Mirena. Also consider the possibility of ectopic pregnancy in the case of lower abdominal pain, especially in association with missed menses or if an amenorrheic woman starts bleeding. Tell women about the signs of ectopic pregnancy and associated risks, including loss of fertility. Women with a history of ectopic pregnancy, tubal surgery, or pelvic infection carry a higher risk of ectopic pregnancy.

Educate her about PID

Kyleena and Mirena are contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy. IUDs have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. Promptly examine users with complaints of lower abdominal pain or pelvic pain, odorous discharge, unexplained bleeding, fever, genital lesions or sores. Inform women about the possibility of PID and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death. PID is often associated with sexually transmitted infections (STIs); Kyleena and Mirena do not protect against STIs, including HIV. PID may be asymptomatic but still result in tubal damage and its sequelae.

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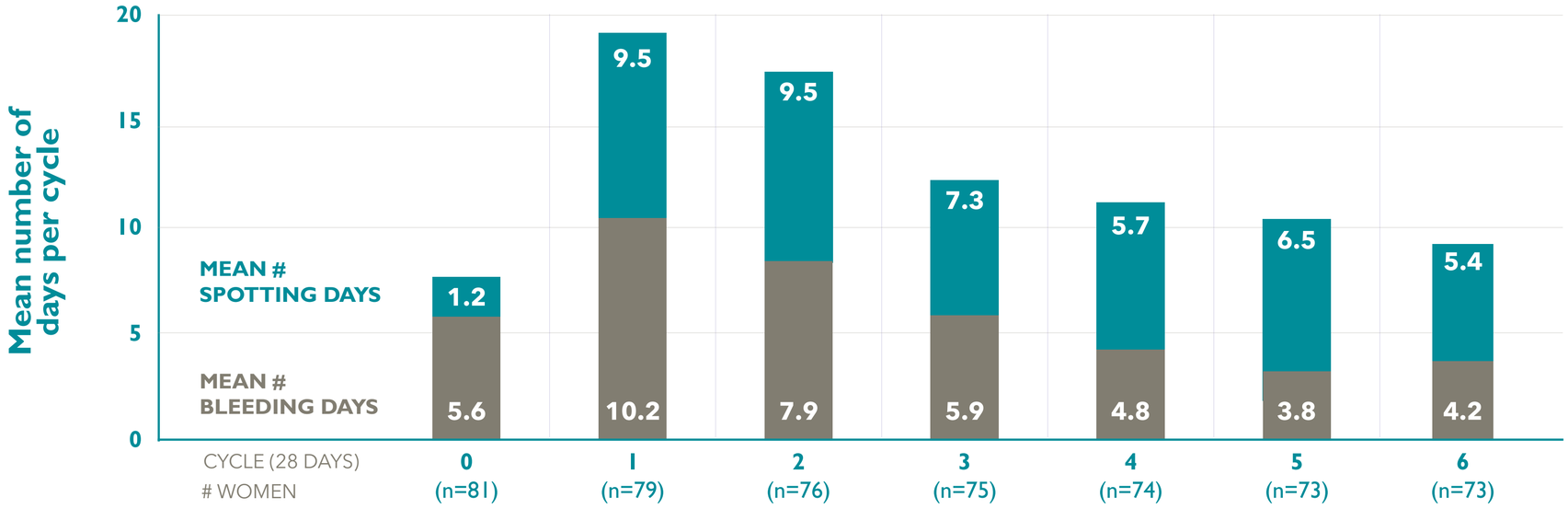
IMPACT OF MIRENA ON BLEEDING AND SPOTTING DAYS IN PATIENTS WITH HMB[2,5]

Randomized, open-label, parallel group, active-control trial comparing the safety and efficacy of Mirena (n=79) to oral hormonal therapy with MPA (n=81) in the treatment of HMB (≥80 mL MBL), over 6 cycles. Women with organic or systemic conditions that can cause heavy uterine bleeding (except for small fibroids—total volume <5 mL) were excluded from the study.[2,5]



- In most women with HMB, the number of bleeding and spotting days may also increase during the initial months of therapy but usually decreases with continued use; the volume of blood loss per cycle progressively becomes reduced[2]

HMB=heavy menstrual bleeding; MBL=menstrual blood loss; MPA=medroxyprogesterone acetate.

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IMPORTANT SAFETY INFORMATION ABOUT KYLEENA AND MIRENA (CONTINUED)

Educate her about PID (continued)

In clinical trials with:

- Kyleena – PID occurred more frequently within the first year and most often within the first month after insertion.
- Mirena – upper genital infections, including PID, occurred more frequently within the first year. In a clinical trial with other IUDs and a clinical trial with an IUD similar to Mirena, the highest rate occurred within the first month after insertion.

Expect changes in bleeding patterns with Kyleena and Mirena

Spotting and irregular or heavy bleeding may occur during the first 3 to 6 months. Periods may become shorter and/or lighter thereafter. Cycles may remain irregular, become infrequent, or even cease. Consider pregnancy if menstruation does not occur within 6 weeks of the onset of previous menstruation.

If a significant change in bleeding develops during prolonged use, take appropriate diagnostic measures to rule out endometrial pathology.

Be aware of other serious complications and most common adverse reactions

Some serious complications with IUDs like Kyleena and Mirena are sepsis, perforation and expulsion. Severe infection, or sepsis, including Group A streptococcal sepsis (GAS) have been reported following insertion of a LNG-releasing IUS. Aseptic technique during insertion of the IUD is essential in order to minimize serious infections, such as GAS.

Perforation (total or partial, including penetration/embedment of Kyleena or Mirena in the uterine wall or cervix) may occur, most often during insertion, although the perforation may not be detected until sometime later. The risk of uterine perforation is increased in women who have recently given birth, and in women who are breastfeeding at the time of insertion. In a large US retrospective, postmarketing safety study of IUDs, the risk of uterine perforation was highest when insertion occurred within ≤6 weeks postpartum and also higher with breastfeeding at the time of insertion. The risk of perforation may be increased if inserted when the uterus is fixed, retroverted or not completely involuted. If perforation occurs, locate and remove the intrauterine system. Surgery may be required. Delayed detection or removal of the intrauterine system in case of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses, and erosion of adjacent viscera. In addition, perforation may reduce contraceptive efficacy and result in pregnancy.

Partial or complete expulsion of Kyleena or Mirena may occur resulting in the loss of contraceptive protection. The risk of expulsion is increased with insertions immediately after delivery and appears to be increased with insertion after second-trimester abortion based on limited data. In the same postmarketing study, the risk of expulsion was lower with breastfeeding status. Remove a partially expelled IUD. If expulsion has occurred, a new Kyleena or Mirena can be inserted any time the provider can be reasonably certain the woman is not pregnant.

Ovarian cysts may occur and are generally asymptomatic, but may be accompanied by pelvic pain or dyspareunia. Evaluate persistent enlarged ovarian cysts.

In clinical trials with:

- Kyleena – the most common adverse reactions (≥5%) were vulvovaginitis (24%), ovarian cyst (22%), abdominal/pelvic pain (21%), headache/migraine (15%), acne/seborrhea (15%), dysmenorrhea/uterine spasm (10%), breast pain/breast discomfort (10%), and increased bleeding (8%).

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A 3-YEAR, PHASE II ANALYSIS OF KYLEENA[6]

A MULTICENTER, RANDOMIZED, OPEN-LABEL, 3-ARM, PHASE II STUDY[6]

Conducted between April 2005 and December 2008, the study objective was to identify an appropriate dose for a new contraceptive LNG-IUS. The efficacy, bleeding profile, and safety of LNG-IUS12, Kyleena (LNG-IUS16), and Mirena were examined in a total of 738 parous or nulliparous women aged 21 to 40 years at 37 sites across 5 European countries. Patients had either LNG-IUS12 (n=239), Kyleena (n=245), or Mirena (n=254) placed. The primary outcomes measures were pregnancy rate expressed by Pearl Index, bleeding profile, ease and pain of placement and removal, and AEs.

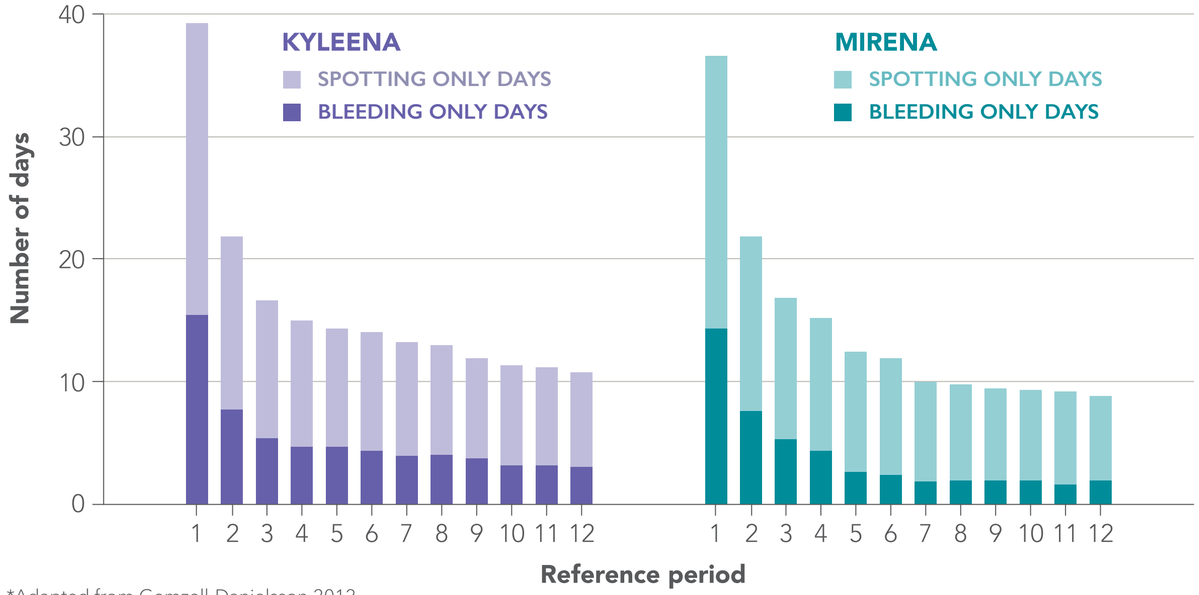
EFFICACY[6]

The 3-year treatment unadjusted Pearl Indices for Kyleena and Mirena were 0.82 and 0.00, respectively.

- 95% upper confidence limits of Kyleena and Mirena were 1.92 and 0.59, respectively. The Kaplan-Meier estimates for the cumulative failure rate during 3 years were 0.025 and 0.000, respectively

AE=adverse event; LNG-IUS=levonorgestrel-releasing intrauterine system.

MEAN NUMBER OF BLEEDING OR SPOTTING DAYS PER 90-DAY REFERENCE PERIOD OVER 3 YEARS[6]*



*Adapted from Gemzell-Danielsson 2012.

Dropouts were not accounted for in this analysis; the results are based on subjects participating during the respective reference period. The dropout rates (for any reason) were 29.0% in the Kyleena arm and 28.3% in the Mirena arm. It is possible that subjects dropping out as a result of changes in bleeding patterns may have influenced these results.[6]

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STUDY RESULTS AND LIMITATIONS[1,2,6]

SAFETY RESULTS[6]

Most frequently reported treatment-related AEs in ≥10% of women in the Kyleena and Mirena arms, respectively: Acne (22.4% and 28.3%), breast discomfort (18.4% and 22.4%), abdominal distention (14.3% and 16.1%), headache (13.1% and 17.3%), increased weight (11.4% and 8.3%), breast pain (11.4% and 7.1%), altered mood (10.2% and 9.8%), and ovarian cysts* (8.6% and 22.0%).

Serious AEs† were reported. In the Kyleena arm, ectopic pregnancy (n=2) and spontaneous abortion (n=1) were reported. In the Mirena arm, ovarian cysts (n=4) and acute severe vaginal bleeding‡ (n=1) were reported.

Treatment-related AEs leading to study withdrawal: 15% (n=37) of women in the Kyleena arm and 17% (n=44) in the Mirena arm.

There were 9 complete or partial expulsions (partial expulsions defined as presence of the device in the cervical canal on ultrasound or gynecological examination) that occurred between the Kyleena (n=5) and Mirena (n=4) arms throughout the study.

POTENTIAL STUDY LIMITATIONS

- European protocols may differ from those of the US[6]
- Low sample size per treatment arm[6]
- Study did not evaluate non-inferiority against Mirena[6]
- Dropouts were not accounted for in the analysis of the bleeding patterns[6]
- Patients were not followed for the product's recommended duration of use[1,2,6]

*Cysts described as abnormal, nonfunctional, and/or >3 cm in diameter.[6]
†Reported by the investigator to be at least possibly related to study treatment.[6]
‡After conization, treated with laser cauterization of a cervical abrasion.[6]

AE=adverse event.

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DISCUSS WITH HER WHICH BAYER IUD MAY BEST FIT HER NEEDS

PATIENTS SEEKING AN IUD FOR LONG-ACTING REVERSIBLE CONTRACEPTION[1,2]

SHE TRUSTS YOU TO HELP HER UNDERSTAND HER OPTIONS AND DETERMINE WHICH IUD MAY BE APPROPRIATE FOR HER

CONTRACEPTION ONLY

Talk to your patient about Kyleena® (levonorgestrel-releasing intrauterine system) 19.5 mg

Kyleena is indicated for the prevention of pregnancy for up to 5 years. Replace the system after 5 years if continued use is desired.

HEAVY MENSTRUAL BLEEDING

Talk to your patient about Mirena® (levonorgestrel-releasing intrauterine system) 52 mg

Mirena is indicated for prevention of pregnancy for up to 7 years; replace after the end of the seventh year. Mirena is indicated for the treatment of HMB for up to 5 years in women who choose to use intrauterine contraception as their method of contraception; replace after the end of the fifth year if continued treatment of HMB is needed.

HMB=heavy menstrual bleeding; IUD=intrauterine device.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA AND MIRENA (CONTINUED)

Be aware of other serious complications and most common adverse reactions (continued)

- Mirena
  - Adverse reactions reported in ≥5% users are alterations of menstrual bleeding patterns [including unscheduled uterine bleeding (31.9%), decreased uterine bleeding (23.4%), increased scheduled uterine bleeding (11.9%), and female genital tract bleeding (3.5%)], abdominal/pelvic pain (22.6%), amenorrhea (18.4%), headache/migraine (16.3%), genital discharge (14.9%), vulvovaginitis (10.5%), breast pain (8.5%), back pain (7.9%), benign ovarian cyst and associated complications (7.5%), acne (6.8%), depression/depressive mood (6.4%) and dysmenorrhea (6.4%).
  - A separate study with 362 women who have used Mirena for more than 5 years showed a consistent adverse reaction profile in Years 6 and 7. By the end of Year 7 of use, amenorrhea and infrequent bleeding are experienced by 28% and 26% of users, respectively; irregular bleeding occurs in 12%, frequent bleeding in 8% and prolonged bleeding in 2% of users. In this study 6% of women reported the adverse event of weight gain, it is unknown if the weight gain was caused by Mirena.

Teach patients to recognize and immediately report signs or symptoms of the aforementioned conditions. Evaluate patients 4 to 6 weeks after insertion of Kyleena or Mirena and then yearly or more often if clinically indicated.

For important information about Kyleena, please click for the accompanying full Prescribing Information.

For important information about Mirena, please click for the accompanying full Prescribing Information.

References: 1. Kyleena [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; 2018. **2.** Mirena [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; 2020. **3.** Data on file. Bayer HealthCare Pharmaceuticals. Clinical study report. PH-40171. September 2017. **4.** Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception*. 1994;49(1):56-72. **5.** Data on file. Bayer HealthCare Pharmaceuticals. Clinical study report: A38313. January 2009. **6.** Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. *Fertil Steril*. 2012;97(3):616-622.