Kyleena®
(levonorgestrel-releasing intrauterine system) 19.5 mg

Women want a low-dose birth control option. Talk to your appropriate patients about

Kyleena: the smallest, lowest-dose 5-year intrauterine device (IUD)

IN AN ONLINE SURVEY OF 1000 WOMEN CONSIDERING HORMONAL BIRTH CONTROL[1]

50% **OF WOMEN SURVEYED SAID THEY WERE OPEN TO USING AN IUD**

Survey respondents (N=1000) were asked to rate their level of agreement on statements regarding hormonal IUDs on a 7-point scale, with 1 representing "Completely Disagree" and 7 representing "Completely Agree." Results captured 5 and above.

67% **OF THOSE WOMEN WOULD LIKE TO HAVE A LOW-DOSE OPTION**

Survey respondents were asked "When considering a birth control method such as an IUD, do you want a low-dose hormonal option?" Respondents responded using a 7-point scale, with 1 representing "Not At All" and 7 representing "Very Much So." Results captured 5 and above.

The survey conducted by Bayer in September 2019 included women aged 18-44 who were **currently taking or considering taking hormonal prescription birth control** in the next 12 months.

WITH KYLEENA: HIGH CONTRACEPTIVE EFFICACY MAINTAINED OVER 5 YEARS[2]

- 98.6% cumulative efficacy over 5 years
- 99.8% efficacy at year 1
- >99% efficacy for each year of use

The efficacy of Kyleena over 5 years was studied in 1452 parous and nulliparous women aged 18-35.

Year 1: Pearl Index of 0.16; 95% upper confidence limit (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%.

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.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA

Who is not appropriate for Kyleena

Use of Kyleena 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 neoplasia; liver disease, including tumors; untreated acute cervicitis or vaginitis, including lower

For additional Important Safety Information, please see throughout.
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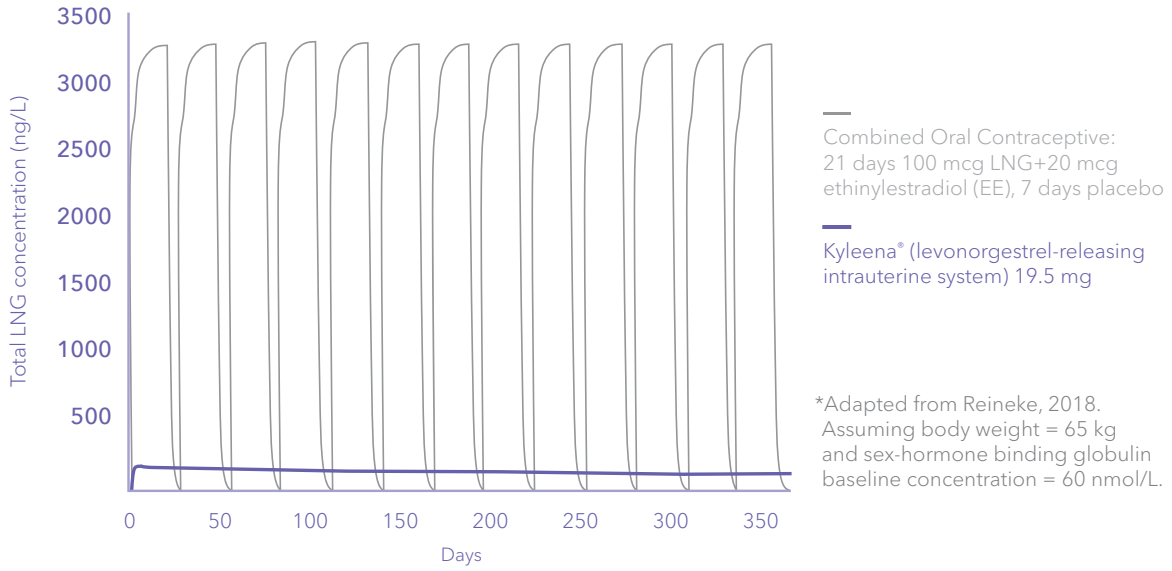
BAYER

KYLEENA ACTS LOCALLY AND PROVIDES LOW HORMONE LEVELS

COMPARISON OF SIMULATED TYPICAL SERUM LEVONORGESTREL (LNG) CONCENTRATIONS[3]*



*Adapted from Reineke, 2018. Assuming body weight = 65 kg and sex-hormone binding globulin baseline concentration = 60 nmol/L.

KYLEENA PROVIDES LOW DAILY RELEASE RATES[1]

	KYLEENA (levonorgestrel-releasing intrauterine system) 19.5 mg
Initial Release Rate	**17.5 mcg/day after 24 days[4]**
After Year 1	**9.8 mcg/day[4]**
Average in Vivo Release Rate	**9.0 mcg/day over 5 years[4]**

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

Who is not appropriate for Kyleena (continued)

genital tract infections (e.g., 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.

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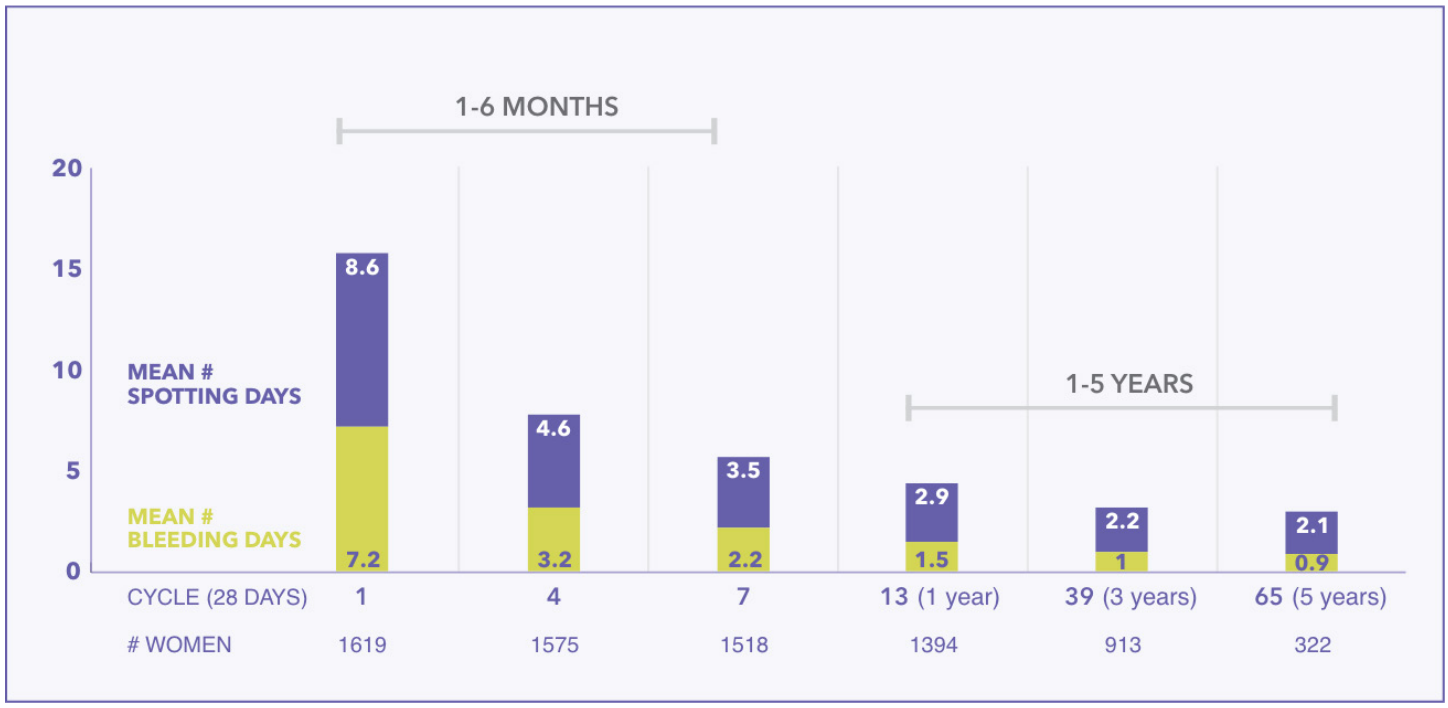
COUNSEL YOUR PATIENTS THAT THEY MAY EXPERIENCE SHORTER, LIGHTER PERIODS AFTER THE FIRST 3 TO 6 MONTHS WITH KYLEENA[1]

- In the first 3 to 6 months of Kyleena use, 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, but bleeding patterns may remain irregular.

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



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

BLEEDING PATTERNS FROM CLINICAL TRIALS (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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THE KYLEENA SATISFACTION STUDY (KYSS)

STUDY DESIGN

This prospective, noninterventional, multinational, single-arm cohort study took place in Belgium, Canada, Germany, Mexico, Norway, Sweden, Spain, and the United States (US). All participants were women with different or no previously used contraceptive methods (including women without previous contraception forming one of the subgroups) who had already decided to use Kyleena®. In the US, the study was conducted at 12 sites in 100 women. In Belgium, Canada, Mexico, Norway, Sweden, and Spain, the sample size was N = 100 in each country. Germany contained the largest sample size of N = 500. The primary objective was to evaluate overall satisfaction with Kyleena at the end of the observation period (12 months) in subgroups of women with different previously used contraceptive methods and different motivations for choosing Kyleena. The secondary objectives included evaluating pain severity at Kyleena insertion, ease of Kyleena insertion (investigator assessed), and satisfaction with the menstrual bleeding profile with Kyleena approximately 4-12 weeks after insertion and at the end of the observation period (12 months).

KYSS PARTICIPANTS WERE ASKED 2 QUESTIONS PERTAINING TO THEIR CONTRACEPTION USAGE BEFORE HAVING KYLEENA PLACED[5]:

Why did you decide to stop your previous method of contraception?

Participants were asked to select one of the following options as a main reason:

1. Afraid the contraceptive method might not be very effective (eg, you had to use emergency contraception)
2. Problems with daily, weekly, or monthly contraceptive routine (intake, insertion, injection, application)
3. Dissatisfaction with the bleeding pattern
4. Dissatisfaction that the contraceptive method was to be taken orally, had to be inserted under the skin, had to be injected, or had to be applied to the skin
5. Fear of potential side effects
6. Contraindication that newly emerged
7. Interactions with other drugs that you have been prescribed or that you take without prescription
8. Other, please specify

Why did you decide to use Kyleena for contraception?

Participants were asked to select one of the following options as a main reason:

1. High contraceptive reliability
2. No daily, weekly, or monthly contraceptive routine (intake, insertion, injection, application)
3. Expectation of shorter, lighter, and less frequent bleeding episodes
4. Acts mainly locally
5. Low hormone dose
6. Estrogen free contraception
7. Small size
8. Minimal drug interactions
9. Other, please specify

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

Clinical considerations for use and removal of Kyleena

Use Kyleena 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:

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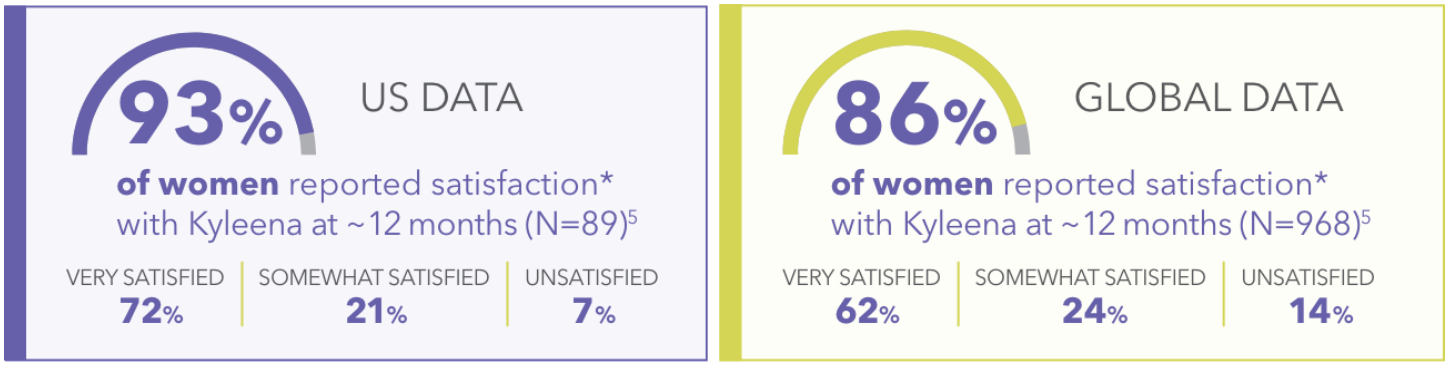
OVERALL SATISFACTION WITH KYLEENA[5]

SATISFACTION WITH KYLEENA, EVALUATED AS THE PRIMARY ENDPOINT, AS OBTAINED FROM THE PATIENT QUESTIONNAIRE: *HOW SATISFIED ARE YOU WITH KYLEENA?*

Results were taken after 12 months or premature discontinuation



*Satisfaction is defined as sum of women reported "very satisfied" or "somewhat satisfied"; "unsatisfied" is defined as sum of women reported "neither satisfied nor dissatisfied," "dissatisfied," or "very dissatisfied."

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

Clinical considerations for use and removal of Kyleena (continue)

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 is displaced (e.g., expelled or perforated the uterus), remove it. Kyleena can be safely scanned with MRI only under specific conditions.

Pregnancy related risks with Kyleena

If pregnancy should occur with Kyleena 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. 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 is 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 does not protect against STIs, including HIV. PID may be asymptomatic but still result in tubal damage and its sequelae.

In clinical trials with Kyleena PID occurred more frequently within the first year and most often within the first month after insertion.

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SATISFACTION RATE WITH KYLEENA IN WOMEN OF ALL AGES BY PARITY

SATISFACTION WITH KYLEENA AS OBTAINED FROM THE PATIENT QUESTIONNAIRE: *HOW SATISFIED ARE YOU WITH KYLEENA?*

Results were taken after 12 months or premature discontinuation

NULLIPAROUS

94% US DATA

of women reported satisfaction* with Kyleena at ~12 months (N=65)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
77%	17%	6%

NULLIPAROUS

87% GLOBAL DATA

of women reported satisfaction* with Kyleena at ~12 months (N=491)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
62%	26%	13%

PAROUS

92% US DATA

of women reported satisfaction* with Kyleena at ~12 months (N=24)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
58%	33%	8%

PAROUS

85% GLOBAL DATA

of women reported satisfaction* with Kyleena at ~12 months (N=477)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
63%	22%	15%

*Satisfaction is defined as sum of women reported "very satisfied" or "somewhat satisfied"; "unsatisfied" is defined as sum of women reported "neither satisfied nor dissatisfied," "dissatisfied," or "very dissatisfied."

AGE DEMOGRAPHICS

US DATA (N=100)[5]	≤17: 3%	18-25: 54%	26-35: 29%	>35: 14%
GLOBAL DATA (N=1126)[5]	≤17: 3%	18-25: 36%	26-35: 32%	>35: 30%

Safety and efficacy of Kyleena have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

Expect changes in bleeding patterns with Kyleena

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.

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PATIENT SATISFACTION ASSESSMENT OF BLEEDING PATTERN WITH KYLEENA

SATISFACTION WITH KYLEENA AS OBTAINED FROM THE PATIENT QUESTIONNAIRE:
HAVE YOU EXPERIENCED MENSTRUAL BLEEDING SINCE KYLEENA PLACEMENT?
(A) IF YES, HOW SATISFIED WERE YOU WITH YOUR MENSTRUAL BLEEDING PATTERN?
(B) IF NO, HOW SATISFIED WERE YOU WITH THE ABSENCE OF MENSTRUAL BLEEDING?

Results were taken after 12 months or premature discontinuation

US DATA

in the US reported satisfaction* with bleeding pattern with Kyleena at ~12 months (N=80)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
48%	33%	20%

GLOBAL DATA

globally reported satisfaction* with bleeding pattern with Kyleena at ~12 months (N=887)[5]

VERY SATISFIED	SOMEWHAT SATISFIED	UNSATISFIED
48%	23%	29%

*Satisfaction is defined as sum of women reported "very satisfied" or "somewhat satisfied"; "unsatisfied" is defined as sum of women reported "neither satisfied nor dissatisfied," "dissatisfied," or "very dissatisfied."

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

Be aware of other serious complications and most common adverse reactions

Some serious complications with IUDs like Kyleena 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 Kyleena is essential in order to minimize serious infections, such as GAS.

Perforation (total or partial, including penetration/embedment of Kyleena 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 Kyleena. Surgery may be required. Delayed detection or removal of Kyleena 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 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 can be inserted any time the provider can be reasonably certain the woman is not pregnant.

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EASE OF INSERTION WITH KYLEENA

KYLEENA SATISFACTION STUDY: SECONDARY ENDPOINTS

Ease of Insertion

Ease of insertion was a secondary endpoint, assessed by investigator at initial visit as easy, slightly difficult, or very difficult.

US DATA

90% **of 100 insertions were rated as "easy" by investigators**[5]

7% of 100 insertions were rated as "slightly difficult" by investigators[5]

3% of 100 insertions were rated as "very difficult" by investigators[5]

There were 24 patients who reported at least 1 adverse event in the US.

GLOBAL DATA

91% **of 1110 insertions were rated as "easy" by investigators**[5]

8% of 1110 insertions were rated as "slightly difficult" by investigators[5]

1% of 1110 insertions were rated as "very difficult" by investigators[5]

Insertion may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, bradycardia) or with seizure, especially in patients with a predisposition to these conditions. Consider administering analgesics prior to insertion.

Pain at Insertion

US DATA

98% **of women** (n=98) rated pain at insertion as none to moderate at initial visit:

Secondary endpoint categories:

NONE	MILD	MODERATE	SEVERE
27%	45%	26%	2%

GLOBAL DATA

96% **of women** (n=1063) rated pain at insertion as none to moderate at initial visit:

Secondary endpoint categories:

NONE	MILD	MODERATE	SEVERE
32%	46%	18%	4%

Counsel on insertion pain: let your patients know that pain is a common side effect. Patients may experience pain, bleeding, or dizziness during and after placement. If symptoms don't pass within 30 minutes after placement, Kyleena may not have been placed correctly. The HCP should examine whether or not Kyleena will need to be removed or replaced.

STUDY DESIGN

Prospective, noninterventional, multinational, single-arm cohort study at 12 sites in 100 women in the US and 1110 women globally with different or no previously used contraceptive methods (including women without previous contraception forming one of the subgroups) who had already decided to use Kyleena.[5,7]

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

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

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

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SAFETY RESULTS AND LIMITATIONS FROM THE KYSS STUDY

TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs) REPORTED IN ≥1% OF WOMEN WHO RECEIVED KYLEENA IN KYSS (N=1129)

ADVERSE EVENT	n (%)
Reproductive system and breast disorders	89 (7.9%)
Vaginal hemorrhage	21 (1.9%)
Dysmenorrhea	11 (1.0%)
Menorrhagia	11 (1.0%)
Gastrointestinal disorders	29 (2.6%)
Abdominal pain lower	16 (1.4%)
Psychiatric disorders	13 (1.2%)
Skin and subcutaneous tissue disorders	13 (1.2%)

Women who were using Kyleena most frequently reported TEAEs related to the reproductive system and breast disorders (89 patients, 7.9%), gastrointestinal disorders (29 patients, 2.6%), psychiatric disorders (13 patients,1.2%), and skin and subcutaneous tissue disorders (13 patients, 1.2%). The most frequently reported TEAEs in women using Kyleena were vaginal hemorrhage (21 patients, 1.9%) and lower abdominal pain (16 patients, 1.4%). A total of 69 patients (6.1%) discontinued Kyleena due to TEAEs, 4 of these patients (0.4%) due to treatment-emergent serious adverse events.

POTENTIAL STUDY LIMITATIONS

- Given the noninterventional study design and limitations inherent to observational studies, findings generated from this study are subject to biases, such as selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines
- The study population was enrolled in selected countries and sites that might not be comparable to the nonparticipating population. This might also be a limiting factor in generalizing the results
- Investigators were chosen based on feasibility criteria, which might have resulted in decreased generalizability of the study results
- Selection bias could not be excluded completely because potential study participants were predominantly selected among those who wanted to change their previously used contraceptive method because of unsatisfactory experiences
- Since this kind of bias could not be ruled out, an additional group of women without previous contraception (new starters) were included. Results of this subgroup enabled putting the satisfaction results into the right perspective

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SHE TRUSTS YOUR OPINION: TALK TO HER ABOUT LOW-DOSE KYLEENA

ASK HER:
What do you expect after deciding on a long-acting reversible contraceptive?

COULD KYLEENA BE RIGHT FOR HER?

For additional information and support, please contact your Bayer representative.

To learn more and download resources, including patient education information, visit www.kyleenahcp.com.

IMPORTANT SAFETY INFORMATION ABOUT KYLEENA (continued)

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

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%).

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

For important information about Kyleena, please see the Full Prescribing Information.

References: 1. Kyleena [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; 2021. **2.** Data on file. Bayer HealthCare Pharmaceuticals Inc. Symphony Health; 2010-2020. **3.** Reinecke I, Hofmann B, Mesic E, Drenth H, Garmann D. An integrated population pharmacokinetic analysis to characterize levonorgestrel pharmacokinetics after different administration routes. *J Clin Pharmacol*. 2018;58(12):1639-1654. **4.** Data on file. Bayer HealthCare Pharmaceuticals Inc. InCrowd Inc. Report; 2019. **5.** Data on file. Bayer Healthcare Pharmaceuticals Inc. 19186; Kyleena Satisfaction Study 1.0; 2017. **6.** Data on file. Bayer Healthcare Pharmaceuticals Inc. 19186; Kyleena Satisfaction Study User Questionnaire; 2017. **7.** Data on file. Bayer HealthCare Pharmaceuticals Inc. Clinical Study Report: PH-37274; April 2014.

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