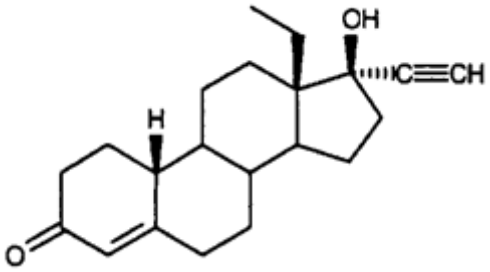
PRODUCT INFORMATION

KYLEENATM

NAME OF THE MEDICINE

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. It is insoluble in water or hexane, slightly soluble in ethanol or acetone, and sparingly soluble in methylene chloride. The chemical name is 13b-ethyl-17β-hydroxy-18, 19-dinor-17a-pregn-4-en-20-yn-3-one. The CAS registry number for levonorgestrel is 797-63-7.



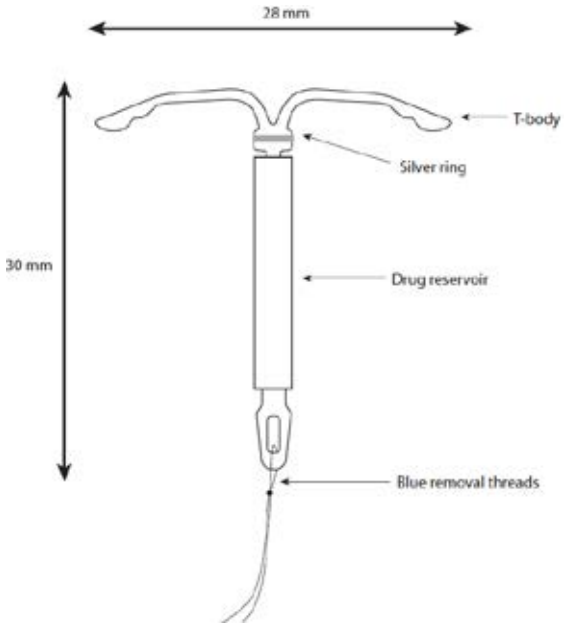
Chemical formula: $C_{21}H_{28}O_2$

Molecular weight: 312.44582 g/mol

DESCRIPTION

Kyleena is an intrauterine delivery system (IUS) that contains 19.5 mg levonorgestrel as the active ingredient.

Kyleena consists of a whitish or pale yellow drug core covered with a semi-opaque membrane, which is mounted on the vertical stem of a T-body. In addition, the vertical stem contains a silver ring located close to the horizontal arms. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Blue coloured removal threads are attached to the loop. The vertical stem of the IUS is loaded in the insertion tube at the tip of the inserter. The inserter consists of a handle and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. The removal threads are located within the insertion tube and handle.



Kyleena contains the following excipients: dimethylsiloxane/methylvinylsiloxane cross linked elastomer, colloidal anhydrous silica, polyethylene, barium sulfate, polypropylene, pigment blue 15 and silver.

PHARMACOLOGY

Pharmacodynamics

Levonorgestrel is a potent progestogen of the 19-nortestosterone class which possesses characteristic gestagenic properties such as endometrial transformation (development of a secretory endometrium), antigonadotropic action and antiestrogenic effects. The antiestrogenic activity of levonorgestrel is not the result of direct estrogen antagonism, since levonorgestrel does not bind to the estrogen receptor *in vitro*, but the result of modification of peripheral estrogenic effects. Levonorgestrel does not possess antiandrogenic or glucocorticoid properties, but does have marked partial androgenic activity.

Levonorgestrel is used in gynaecology as the progestogenic component in combined oral contraceptives and for contraception in progestogen-only pills. Levonorgestrel can also be administered into the uterine cavity with an intrauterine delivery system such as Kyleena. This allows a very low daily dosage, as the hormone is released directly into the uterine cavity.

Kyleena has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates the endometrial synthesis of estrogen and progesterone receptors. The endometrium becomes relatively insensitive to the circulating oestradiol and a strong anti-proliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction were observed during use. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the fallopian tubes inhibits sperm mobility and function, preventing fertilisation.

Pharmacokinetics

Levonorgestrel is released locally into the uterine cavity. Estimated *in vivo* release rates for different points in time are provided in Table 1 below.

Table 1: Estimated *in vivo* release rates

Time	Estimated in vivo release rate (µg/24 hrs)
24 days after insertion	17.5
60 days after insertion	15.3
1 year after insertion	9.8
3 years after insertion	7.9
5 years after insertion	7.4
Average over 5 years	9.0

Absorption

Following insertion, levonorgestrel is released from the IUS into the uterine cavity without delay. More than 90% of the released levonorgestrel is systemically available. Maximum serum concentrations of levonorgestrel are reached within the first two weeks after insertion of Kyleena. Seven days after insertion, a mean levonorgestrel concentration of 162 pg/mL was determined. Thereafter serum concentrations of levonorgestrel decline over time to reach mean concentrations of 91.3 pg/mL after 3 years and 83.1 pg/mL after 5 years. With the use of an levonorgestrel intrauterine delivery system (LNG-IUS), the high local drug exposure in the uterine cavity leads to a strong concentration gradient from the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum >1000-fold).

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to SHBG (sex-hormone-binding globulin). Less than 2% of the circulating levonorgestrel is present as free steroid. Levonorgestrel binds with high affinity to SHBG. Accordingly, changes in the concentration of SHBG in serum result in an increase (at higher SHBG concentrations) or in a decrease (at lower SHBG concentrations) of the total

levonorgestrel concentration in serum together with an opposite change in the proportion of free levonorgestrel. The concentration of SHBG declined on average by about 30% during the first 3 months after insertion of Kyleena and remained relatively stable over the 5 year period of use. The mean apparent volume of distribution of levonorgestrel is about 106 L.

Body weight has also been shown to affect systemic levonorgestrel concentration i.e. low body weight increases levonorgestrel concentration. However, due to the mainly localised action of Kyleena, no impact on the efficacy is expected.

Metabolism

Levonorgestrel is extensively metabolised. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel. The available *in vitro* data suggest that CYP mediated biotransformation reactions may be of minor relevance for levonorgestrel compared to reduction and conjugation.

Excretion

The total clearance of levonorgestrel from plasma is approximately 1.0 mL/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted in faeces and urine at an excretion ratio of about 1. The excretion half-life is about 1 day.

Linearity/Non-linearity

The pharmacokinetics of levonorgestrel are dependent on the concentration of SHBG which itself is influenced by estrogens and androgens. A decrease of SHBG concentration leads to a decrease of total levonorgestrel concentration in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly localised action of Kyleena, no impact on the efficacy of Kyleena is expected.

Paediatric Patients

In a one-year Phase III study in post-menarcheal female adolescents (mean age 16.2, range 12 to 18 years) using another lower-dose LNG-IUS, the pharmacokinetic analysis of 283 adolescents showed estimated levonorgestrel serum concentrations slightly higher (approximately 10%) in adolescents compared to adults. This correlates to the generally lower body weight in adolescents. The ranges estimated for adolescents lie, however, completely within the ranges estimated for adults, showing high similarity.

No differences in the pharmacokinetics of adolescents and adults are expected with Kyleena.

Ethnic Differences

A three-year phase III study in the Asian-Pacific region (93% Asian women, 7% other ethnicities) using another lower-dose LNG-IUS has been performed. A comparison of pharmacokinetic characteristics of levonorgestrel of the Asian population in this study with the Caucasian population from another phase III study showed no clinically relevant difference in systemic exposure and other pharmacokinetic parameters. In addition, the daily release rate of the LNG-IUS was the same in both populations.

No pharmacokinetic differences in women of different ethnicities are expected with Kyleena.

CLINICAL TRIALS

A multicentre, open-label, randomised Phase III study (Report No. PH-37274/Protocol No. 310442) was conducted to evaluate the efficacy and safety of Kyleena in women for long-term reversible contraception. The duration of the study was three years with an optional extension up to five years of use. A total of 1452 women aged 18 to 35 years with an insertion attempt were included in the efficacy and safety assessment of Kyleena for three years with 707 women continuing in the extension phase. Of the 1452 women, 39.5% (574) were nulliparous, of whom 84.0% (482) were nulligravid. The study evaluated contraceptive efficacy with the following parameters: the number of unintended pregnancies, Pearl Index

(PI) and cumulative failure rates, as well as bleeding pattern, pharmacodynamics, pharmacokinetic and safety parameters.

Table 2: PIs by year of treatment for women 18 to 35 years of age and overall 5-year PI, unadjusted, study PH-37274

	No. of women/no. of pregnancies	Relevant exposure time (wy)	Pearl Index (unadj.)	Upper 95% CL
PI by year of treatment and over 5 years, women 18 to 35 years of age[a]				
Year 1 PI	1452 / 2	1252.43	**0.16**	0.58
Year 2 PI	1206 / 4	1066.87	**0.37**	0.96
Year 3 PI	1010 / 4	897.75	**0.45**	1.14
Year 4 PI	773 / 1	659.17	**0.15**	0.85
Year 5 PI	636 / 2	558.30	**0.36**	1.29
5-year PI	1452 / 13	4434.53	**0.29**	0.50

CL = confidence limit, PI = Pearl Index, wy = women years (1 wy = 365 days)

[a] Includes all the women in the study, age range at screening was 18 to 35 years

The one year Pearl Index was 0.16 and the Pearl Index after 5 years was 0.29. The failure rate was approximately 0.2% at 1 year and the cumulative failure rate was approximately 1.4% at 5 years. The failure rate also includes pregnancies due to undetected expulsions and perforations. Because the use of Kyleena does not require daily intake compliance by the users, the pregnancy rates in “typical use” are similar to those observed in controlled clinical trials (“perfect use”). The use of Kyleena does not alter the course of the future fertility.

In the five-year, Phase III study with Kyleena, 116 of 163 women (71.2%) who discontinued because of the wish for pregnancy and for whom follow up was available, had become pregnant during the 12 month follow-up (Report No. PH-38002/Protocol No. 310442).

With Kyleena, the alterations in menstrual patterns are a result of the direct action of levonorgestrel on the endometrium and do not reflect the ovarian cycle. There is no clear difference in follicle development, ovulation or oestradiol and progesterone production in women with different bleeding patterns. In the process of inhibition of the endometrial proliferation, there can be an initial increase of spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in the reduction of the duration and volume of menstrual bleeding during use of Kyleena. Scanty flow frequently develops into oligomenorrhea or amenorrhea. Ovarian function remains normal and oestradiol levels are maintained, even when women are amenorrhoeic.

In clinical trials with Kyleena, ovulation was observed in the majority of the subset of women studied (Report No. PH-37274/Protocol No. 310442 and Report No. A46796/Protocol No. 308901). Evidence of ovulation was seen in 23 out of 26 women in the first year, in 19 out of 20 women in the second year, and in all 16 women in the third year. In the fourth year, evidence of ovulation was observed in the one woman remaining in the subset and in the fifth year, no women remained in this subset.

INDICATIONS

Contraception for up to 5 years.

CONTRAINDICATIONS

- Pregnancy
- Acute or recurrent pelvic inflammatory disease or conditions associated with increased risk for pelvic infections
- Lower genital tract infection
- Postpartum endometritis or infected abortion during the past three months

- Cervicitis
- Cervical intraepithelial neoplasia
- Uterine or cervical malignancy
- Confirmed or suspected hormone dependent tumours including breast cancer
- Abnormal uterine bleeding of unknown etiology
- Congenital or acquired uterine anomaly including fibroids which would interfere with insertion and/or retention of the intrauterine system (i.e. if they distort the uterine cavity)
- Acute liver disease or liver tumour
- Hypersensitivity to the active substance or to any of the excipients

PRECAUTIONS

Kyleena should be used with caution after specialist consultation, or removal of the system should be considered if any of the following conditions exist or arise for the first time:

- migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischaemia
- exceptionally severe headache
- jaundice
- marked increase in blood pressure
- severe arterial disease such as stroke or myocardial infarction
- acute venous thromboembolism

Data on use with Kyleena in nulliparous women is limited to approximately 37% of the study population.

Pelvic Infection

While Kyleena and the inserter are sterile they may, due to bacterial contamination during insertion, become a vehicle for microbial transport in the upper genital tract. Pelvic infection has been reported during use of any IUS or IUD. In clinical trials, pelvic inflammatory disease was observed more frequently at the beginning of Kyleena use, which is consistent with published data for copper IUDs, where the highest rate of pelvic inflammatory disease occurs during the first 3 weeks after insertion and decreases thereafter.

Patients should be fully evaluated for risk factors associated with pelvic infection (e.g. multiple sexual partners, sexually transmitted infections, prior history of PID). Pelvic infections such as pelvic inflammatory disease may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynaecological or surgical procedures, severe infection or sepsis (including group A *Streptococcal* sepsis) can occur following IUD insertion.

If a woman experiences recurrent endometritis or pelvic inflammatory disease or if an acute infection is severe or does not respond to treatment, Kyleena must be removed.

Bacteriological examinations are indicated and monitoring is recommended, even with discrete symptoms indicative of infections.

Expulsion

In clinical trials with Kyleena, the incidence of expulsion was low and in the same range as that reported for other IUDs and IUSs. Symptoms of the partial or complete expulsion of Kyleena may include bleeding or pain. However, partial or complete expulsion can occur without the woman noticing it, leading to decrease or loss of contraceptive protection. As Kyleena typically decreases menstrual bleeding over time, an increase of menstrual bleeding may be indicative of an expulsion.

A partially expelled Kyleena should be removed. A new system can be inserted at that time provided pregnancy has been excluded.

A woman should be advised how to check the threads of Kyleena and to contact her healthcare provider if the threads cannot be felt.

Perforation

Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur, most often during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of Kyleena. Excessive pain or bleeding during insertion or while Kyleena is *in situ* may be indicative of a perforation. Such occurrences and/or lost threads should be further investigated. Should a perforation occur, the system must be removed as soon as possible, surgery may be required.

In a large, prospective, comparative, non-interventional cohort study in users of other IUDs (n=61,448 women), the incidence of perforation was 1.3 (95% CI: 1.1-1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1000 insertions in the cohort of another LNG-IUS, and 1.1 (95% CI: 0.7-1.6) per 1000 insertions in the copper IUD cohort.

The study showed that both breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 3). These risk factors were independent of the type of IUD inserted.

Table 3: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women)

	Breastfeeding at time of insertion	**Not breastfeeding at time of insertion**
Insertion ≤ 36 weeks after delivery	5.6 (95% CI: 3.9-7.9; n=6,047 insertions)	1.7 (95% CI: 0.8-3.1; 5,927 insertions)
Insertion ≥ 36 weeks after delivery	1.6 (95% CI: 0.0-9.1; n=608 insertions)	0.7 (95% CI: 0.5-1.1; n=41,910 insertions)

The risk of perforations may be increased in women with fixed retroverted uterus.

Re-examination after insertion should follow the guidance given under the heading “Medical Examination” (see DOSAGE AND ADMINISTRATION), which may be adapted as clinically indicated in women with risk factors for perforation.

Ectopic Pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry an increased risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding. Women who become pregnant while using Kyleena should be evaluated for ectopic pregnancy. The absolute risk of ectopic pregnancy in Kyleena users is low. However, when a woman becomes pregnant with Kyleena *in situ*, the relative likelihood of this pregnancy being ectopic is increased and urgent assessment is required (see ADVERSE EFFECTS). In the event of an unplanned pregnancy, see also “Use in Pregnancy”.

The overall incidence of ectopic pregnancy with Kyleena is approximately 0.20 per 100 women-years. This rate is lower than in women not using any contraception (0.3-0.5 per 100 women years).

Sexually Transmitted Infections

Kyleena does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs). The woman should be advised that additional measures, e.g. condoms, are needed to prevent the transmission of STIs.

Lost Threads

If the removal threads are not visible at the cervix on follow-up examinations, pregnancy must be excluded. The threads may have been drawn up into the uterus or cervical canal and may reappear

during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing the cervical canal with a suitable instrument. If they cannot be found, the possibility of expulsion or perforation should be considered. Ultrasound examination may be used to ascertain the position of the system. If ultrasound is not available or is not successful, X-ray may be used to locate Kyleena.

Ovarian Cysts/Enlarged Ovarian Follicles

Since the contraceptive effect of Kyleena is mainly due to its local effects within the uterus, there is generally no change in ovulatory function, including regular follicular development, oocyte release and follicular atresia in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Ovarian cysts (including haemorrhagic and ruptured ovarian cysts) have been reported over the course of the clinical trials as an adverse event at least once in approximately 22.2% of women using Kyleena. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases, the enlarged follicles resolve spontaneously over two to three months' observation. Should an enlarged follicle fail to resolve spontaneously, continued ultrasound monitoring and other diagnostic/therapeutic measures may be appropriate. Rarely, surgical intervention may be required.

Magnetic Resonance Imaging (MRI)

Non-clinical testing of **another LNG-IUS with the same size silver ring and T-body has demonstrated that a patient** may be scanned after placement of Kyleena ('MR conditional') under the following conditions:

- Static magnetic field of 3-Tesla or less,
- Spatial gradient field of 36,000 Gauss/cm (360 T/m) or less
- Maximum whole body averaged specific absorption rate (SAR) of 4W/kg in the First Level Controlled mode for 15 minutes of continuous scanning

In non-clinical testing, the aforementioned LNG-IUS produced a temperature rise of equal or less than 1.8°C at a maximum whole body averaged specific absorption rate (SAR) of 2.9 W/kg, for 15 minutes of MR scanning at 3T using a transit/receive body coil. A small amount of imaging artefact may occur if the area of interest is in the same area or relatively close to the position of Kyleena.

No clinical data are currently available in women using Kyleena undergoing MRI.

Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. An individual benefit-risk assessment should be made in women in whom breast cancer is diagnosed while using Kyleena. Removal of Kyleena should be considered.

Irregular bleeding may be a symptom of underlying pathologies such as endometrial polyps, hyperplasia or cancer. Endometrial pathology should therefore be excluded before insertion of Kyleena (see also Medical Examination/Consultation).

Heart Disease

Kyleena should be used with caution in women who have congenital heart disease or valvular heart disease and who are at risk of infective endocarditis. It is recommended that physicians consult local guidelines with regards to antibiotic prophylaxis during insertion and removal.

Diabetes

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Kyleena. However, there is generally no need to alter the therapeutic regimen in Type I diabetics using LNG-IUS.

Infrequent Bleeding

Infrequent bleeding and/or amenorrhea develops gradually. By the end of the fifth year about 26.4% and 22.6% of the users developed infrequent bleeding and/or amenorrhoea, respectively. Pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. A repeated pregnancy test is not necessary in subjects who remain amenorrhoeic unless indicated by other signs of pregnancy.

Effects on Fertility

The use of an LNG-IUS does not alter the course of future fertility. Upon removal of the LNG-IUS, women return to their normal fertility (see Pharmacodynamics).

Use in Pregnancy (Category B3)

The insertion of Kyleena in pregnant women is contraindicated (see CONTRAINDICATIONS).

Because of the intrauterine administration and the local exposure to levonorgestrel, the possible occurrence of virilising effects in a female fetus should be taken into consideration. Clinical experience of the outcomes of pregnancies under Kyleena treatment is limited due to the high contraceptive efficacy. Women should be informed that, to date, there is no evidence of birth defects caused by LNG-IUS use in cases where pregnancy continues to term with the LNG-IUS in place.

When levonorgestrel-impregnated silastic devices were introduced into the uteri of pregnant rabbits, the incidence of late fetal resorption was increased when compared to sham-operated controls. There were no other effects on the fetuses that could be attributed specifically to the device or to levonorgestrel.

Unplanned Pregnancy

Kyleena, when inserted according to the insertion instructions, has a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 1.4% at 5 years. The failure rate also includes pregnancies due to undetected expulsions and uterine perforations.

If a woman becomes pregnant while using Kyleena, removal of the system is recommended since any intrauterine contraceptive left *in situ* may increase the risk of abortion and pre-term labour. Removal of Kyleena or probing of the uterus may also result in spontaneous abortion. Ectopic pregnancy should be excluded. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Use in Lactation

In general, there appears to be no deleterious effect on infant growth or development when using any progestogen-only method after six weeks postpartum. An LNG-IUS does not affect the quantity or quality of breast milk. Small amounts of progestogen (about 0.1 % of the levonorgestrel dose) pass into the breast milk in nursing mothers.

Paediatric Use

Safety and efficacy of Kyleena has been studied in women aged 18 and over. Safety and efficacy is expected to be the same for post-menarcheal adolescents under the age of 18 as for users 18 years and older. The safety profile of another lower-dose LNG-IUS observed in a study of 304 adolescents was consistent with that in the adult population (see Pharmacodynamics). Kyleena is not indicated for use before menarche.

Use in the Elderly

There is no indication for the use of Kyleena in postmenopausal women.

Patients with Hepatic Impairment

Kyleena has not been studied in women with hepatic impairment. Kyleena is contraindicated in women with acute liver disease or liver tumour (see CONTRAINDICATIONS).

Patients with Renal Impairment

Kyleena has not been studied in women with renal impairment.

Genotoxicity

The genotoxic potential of levonorgestrel has not been fully investigated, although limited data available to date suggest that it does not appear to be genotoxic. Saline, water, ethanol and/or DMSO extracts of the silver ring, elastomer, polyethylene, polypropylene or drug-elastomer components of Kyleena were without mutagenic activity in bacteria. Further assays for genotoxicity (*e.g.*, mouse lymphoma assay, *in vivo* micronucleus test) conducted with extracts of the device materials, were also negative.

Carcinogenicity

No studies on the carcinogenic potential of Kyleena have been performed.

A long-term study with orally administered levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism. The clinical relevance of these findings is uncertain.

It should be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing levonorgestrel. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The contribution of the progestogen component of oral contraceptives to the development of hepatic adenomas is not known.

INTERACTIONS WITH OTHER MEDICINES

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones.

Substances increasing the clearance of levonorgestrel, e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St John's wort.

The influence of these medicines on the contraceptive efficacy of Kyleena is not known, but it is not believed to be of major importance due to the local mechanism of action.

Substances with variable effects on the clearance of levonorgestrel, e.g.:

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestogen.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors):

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestogen.

ADVERSE EFFECTS

The majority of women experience changes in menstrual bleeding pattern after insertion of Kyleena. Over time, the frequency of amenorrhoea and infrequent bleeding increases, and the frequency of prolonged, irregular and frequent bleeding decreases. The following bleeding patterns were observed in clinical trials with Kyleena:

Table 4: Bleeding patterns by 90-day reference period

	First 90 days (%)	Second 90 days (%)	End of Year 1 (%)	End of Year 3 (%)	End of Year 5 (%)
Amenorrhoea	< 1	5	12	20	23
Infrequent bleeding	10	20	26	26	26
Frequent bleeding	25	10	4	2	2
Prolonged bleeding*	57	14	6	2	1
Irregular bleeding	43	25	17	10	9

*Subjects with prolonged bleeding may also be included in one of the other categories (excl. amenorrhea).

The frequencies of adverse drug reactions (ADRs) reported with Kyleena are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are crude incidences of the events observed in clinical trials for the indication contraception in 1697 women (5225.52 women-years) using Kyleena.

Frequencies are defined as:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)

Table 5: Adverse reactions in Phase II and III clinical trials

System Organ Class (MedDRA)	Very Common	Common	Uncommon	Rare
Psychiatric disorders		Depressed mood/ Depression		
Nervous system disorders	Headache	Migraine		
Gastrointestinal disorders	Abdominal/ pelvic pain	Nausea		
Skin and subcutaneous tissue disorders	Acne/ Seborrhoea	Alopecia	Hirsutism	
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Ovarian cyst* Vulvovaginitis	Upper genital tract infection Dysmenorrhea Breast pain/ discomfort Device expulsion (complete and partial) Genital discharge		Uterine perforation**

* Ovarian cysts had to be reported as AEs if they were abnormal, non-functional cysts and/or had a diameter > 3 cm on ultrasound examination.

** This frequency is based on clinical trials that excluded breastfeeding women. In a large, prospective, comparative, non-interventional cohort study with women using another LNG-IUS and copper IUDs, the frequency of perforation in women who were breastfeeding or had an insertion up to 36 weeks after delivery was “uncommon” (see PRECAUTIONS).

With the use of another LNG-IUS, cases of hypersensitivity including rash, urticaria and angioedema have been reported.

If a woman becomes pregnant while using Kyleena, the relative risk of ectopic pregnancy is increased.

The removal threads may be felt by the partner during intercourse.

The following ADRs have been reported in connection with the insertion or removal procedure of Kyleena: Procedural pain, procedural bleeding, insertion-related vasovagal reaction with dizziness or syncope. The procedure may precipitate a seizure in an epileptic patient.

For other IUDs, cases of sepsis (including group A *Streptococcal* sepsis) have been reported following insertion (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Kyleena is inserted into the uterine cavity and is effective for up to five years.

The *in vivo* release rate is approximately 17.5 µg/24 hours after 24 days and is reduced to approximately 15.3 µg/24 hours after 60 days and to 9.8 µg/24 hours after one year. It then declines progressively to 7.4 µg/24 hours after five years. The average levonorgestrel *in vivo* release rate is approximately 9 µg/24 hours over the period of five years.

Care must therefore be given to adequate training in the correct insertion technique and the availability of appropriate instruments for the insertion of Kyleena. For further information regarding training providers, please contact Bayer Australia Ltd.

Medical Examination/Consultation

Before insertion, the woman must be informed of the efficacy, risks and side effects of Kyleena. A physical examination including pelvic examination and examination of the breasts should be conducted. A cervical smear should be performed as needed, according to the Healthcare Professional’s evaluation. Standard testing procedures should be used to exclude pregnancy and sexually transmitted infections. Genital infections must have been successfully treated prior to insertion. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of Kyleena is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximise efficacy. Therefore, the instructions for insertion should be followed carefully.

Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient. The woman should be re-examined 4 to 12 weeks after insertion including performing a pelvic exam, checking for pelvic tenderness, inserting a speculum and checking the length of the threads. Follow-up should continue once a year thereafter or more frequently if clinically indicated.

Irregular bleeding and spotting are common in the first months of therapy with all LNG-IUSs including Kyleena. If bleeding becomes heavier and/or more irregular over time, appropriate diagnostic measures should be taken as irregular bleeding may be a symptom of endometrial polyps, hyperplasia or cancer.

Insertion and Removal/Replacement

It is recommended that healthcare providers keep a record of the insertion of the device including batch number in the patient’s medical records.

Emphasis should be given to training in the correct insertion technique. It is recommended that Kyleena should only be inserted by physicians/healthcare professionals who are experienced in IUS insertions and/or have undergone training on the Kyleena insertion procedure.

Kyleena is to be inserted into the uterine cavity within seven days of the onset of menstruation. Kyleena can be replaced by a new system at any time in the cycle. Kyleena can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum.

In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, appropriate steps should be taken immediately to exclude perforation, such as physical examination and ultrasound.

Kyleena is not suitable for use as a post-coital contraceptive.

Kyleena can be distinguished from other IUSs by the visibility of the silver ring on ultrasound and the blue colour of the removal threads. The T-frame of Kyleena contains barium sulfate which makes it visible in X-ray examination.

Kyleena is removed by gently pulling on the threads with forceps. If the threads are not visible and the system is found to be in the uterine cavity on ultrasound examination, it may be removed using narrow forceps. This may require dilatation of the cervical canal or surgical intervention.

The system should be removed no later than by the end of the fifth year. If the woman wishes to continue using the same method, a new system can be inserted immediately following removal of the original system.

If pregnancy is not desired, the removal should be carried out within seven days of the onset of menstruation, provided the woman is still experiencing regular menses. If the system is removed at some other time during the cycle or the woman does not experience regular menses and the woman has had intercourse within a week, she is at risk of pregnancy. To ensure continuous contraception, a new system should be immediately inserted or an alternative contraceptive method should have been initiated.

After removal of Kyleena, the system should be examined to ensure that it is intact.

Instructions for Use/Handling

Kyleena is supplied in a sterile package within an integrated inserter that enables single handed loading. The package should not be opened until required for insertion. The exposed product should be handled using aseptic techniques. If the seal of the sterile package is broken, or appears compromised, the product should not be used.

Special instructions for insertion are in the package.

Kyleena is supplied with a patient reminder card in the outer package. Complete the patient reminder card and give it to the patient after insertion.

OVERDOSAGE

Not applicable for this product.

PRESENTATION AND STORAGE CONDITIONS

Kyleena is supplied within an integrated inserter in a sterile package, which should not be opened until needed for insertion. Do not re-sterilise. Kyleena is for single use only. Do not use if the inner package is damaged or open. Do not insert after the expiry month and year shown on the label.

A discarded or removed IUS should be treated as medicinal waste, since it may contain hormone remnants.

Each pack contains one intrauterine system. Kyleena is packaged in a polyethylene terephthalate glycol (PETG) thermoformed blister package with a peelable polyethylene lid.

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714

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Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

18 January 2017

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