SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
KYLEENA

Intrauterine delivery system

COMPOSITION:
Active: Levonorgestrel. Each sterile intrauterine system contains anhydrous and micronized levonorgestrel 19,5 mg.
Inactives: Barium sulphate; copper phthalocyanine; polydimethylsiloxane elastomer; polyethylene; polypropylene; silica colloidal anhydrous; silver.

PHARMACOLOGICAL CLASSIFICATION:
A. 32.9. Other – Intrauterine devices.

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Levonorgestrel has local progestogenic effects in the uterine cavity. Levonorgestrel in the endometrium down-regulates endometrial oestrogen and progesterone receptors.
The endometrium becomes relatively insensitive to the circulating estradiol resulting in an antiproliferative effect and thickening of the cervical mucus.

Morphological changes of the endometrium and a weak local foreign body reaction were observed during use.

The thickening of the cervical mucus prevents passage of the sperm through the cervical canal resulting in inhibition of sperm mobility thereby preventing fertilisation.
In clinical trials with KYLEENA, ovulation was observed in the majority of the subject studied.

The contraceptive efficacy of KYLEENA has been evaluated in a clinical study with 1452 women aged 18 to 35 including 39,5 % (574) nulliparous women of whom 84,0 % (482) were nulligravid.

The 1 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 1,5 % at 5 years. The failure rate also includes pregnancies due to undetected expulsion and uterine perforations.

In a 5 year study with KYLEENA, 116 out of 163 (71,2 %) women who discontinued because of the wish for pregnancy and with follow-up information available, had become pregnant during the 12 month follow-up.

With KYLEENA, the alteration in menstrual patterns are a result of the direct action of levonorgestrel on the endometrium and do not affect 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 in spotting during the first month of use. Thereafter, suppression of the endometrium results in the reduction of the duration and volume of menstrual bleeding during the use of KYLEENA resulting in oligomenorrhoea or amenorrhoea.

Pharmacokinetic properties:
Levonorgestrel is released locally into the uterine cavity. Estimated *in vivo* delivery rates for different points in time are provided in the table below:

Estimated *in vivo* release rates:

Time	Estimated *in vivo* release rates [µg/ 24 hours]
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 intrauterine system (IUS) into the uterine cavity. More than 90 % of the released LNG 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 serum levonorgestrel concentration of 162 pg/ml was determined. Thereafter serum concentration of levonorgestrel decline over time to reach mean concentration of 91,3 pg/ml after 3 years and 83,1 pg/ml after 5 years.

There is a strong concentration gradient of levonorgestrel from the endometrium to the myometrium (gradient endometrium to myometrium > 100-fold), and to low concentration of levonorgestrel in serum (gradient endometrium to serum > 1000-fold).

Distribution:
Levonorgestrel is bound non-specifically to serum albumin and specifically to sex binding hormone globulin (SHBG). Less than 2 % of the circulating levonorgestrel is present as free steroid. Levonorgestrel binds with high affinity to SHBG. Accordingly, changes in concentration of SHBG in serum result in an increase (at higher SHBG concentrations) or a decrease (at lower SHBG concentrations) of the total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 30 % during the first 3 months after insertion of the IUS and remained relatively stable over the 5 year period of use. The mean apparent volume of distribution of levonorgestrel is about 106 litres.

Biotransformation:
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.
CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel. The available *in vitro* data suggest that CYP mediated biotransformation reaction may be of minor relevance for levonorgestrel compared to reduction and conjugation.

Elimination:
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 1:1. 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 oestrogens 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.

INDICATION:
Contraception for up to 5 years in women 18 years and older.

CONTRAINDICATIONS:
- Hypersensitivity to levonorgestrel or any of the ingredients of KYLEENA
- Pregnancy
- Acute or recurrent pelvic inflammatory disease or conditions associated with increased risk of pelvic infections, including gonorrhoea and other sexually transmitted infections
- Acute cervicitis or vaginitis
- Postpartum endometritis or infected abortion during the past three months

- Cervical neoplasm
- Uterine or cervical malignancy
- Progestogen-dependent tumours
- Abnormal uterine bleeding of unknown aetiology
- 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.

WARNINGS AND SPECIAL PRECAUTIONS:

Medical examination/consultation

Before insertion, the woman must be informed of the benefits and risks of KYLEENA. A physical examination including pelvic examination, examination of the breast and a cervical smear should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional's evaluation. Pregnancy and sexually transmitted diseases should be excluded. Genital infections should be 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 important in order to maximise the efficacy and reduce the risk of expulsion. The instruction for the insertion should be followed carefully. It is recommended that KYLEENA should only be inserted by healthcare professionals who are experienced in IUS insertion and have undergone training on the KYLEENA insertion procedure.

KYLEENA may 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 ischemia
- severe headache
- jaundice
- marked increase in blood pressure
- severe arterial disease such as stroke or myocardial infarction.

KYLEENA may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis.

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of KYLEENA.

Infrequent bleeding/Amenorrhoea

Infrequent bleeding and/or amenorrhoea develop gradually. By the end of the fifth year about 26,4 % and 22,6 % of the users develop 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.

Irregular bleeding and spotting are common in the first month after insert of 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.

Pelvic infection

Pelvic infection has been reported during the use KYLEENA. While KYLEENA and the inserter are sterile they may, due to bacterial contamination during insertion, become a vehicle for microbial transport into the upper genital tract. Pelvic inflammatory disease was observed more frequently at the beginning of KYLEENA use.

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 diseases may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

Severe infections or sepsis (including group A streptococcal sepsis) can occur following KYLEENA insertion.

If a woman experience 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 3,5 %. 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 decreased 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 is excluded.

The woman should be advised how to check for 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 KYLEENA may occur, most often during insertion, and may decrease the effectiveness of KYLEENA. Such a system must be removed.

Breastfeeding at the time of insertion and insertions up to 36 weeks after giving birth are associated with an increased risk of perforation (see Table 1 below).
The risk factors were independent of the type of IUD inserted.

Table 1: 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 to 7,9; n= 6047 insertions	1,7 (95 % CI 0,8 to 3,1; n= 5927 insertions)
Insertion ≥ 36 weeks after delivery	1,6 (95 % CI 0,0 to 9,1; n= 608 insertions)	0,7 (95 % CI 0,5 to 1,1; n= 41910 insertions)

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

Ectopic pregnancy
Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher 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.
When a woman becomes pregnant with KYLEENA in situ, the relative likelihood of ectopic pregnancy is increased.

The overall incidence of ectopic pregnancy with KYLEENA is approximately 0,20 per 100 women years.

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 effect 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 adverse event at least once in approximately 22 % of women using KYLEENA. Most of these follicles were asymptomatic, although some were accompanied by pelvic pain or dyspareunia.

In most cases, the enlarged follicles resolved 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. Surgical intervention may be required in some cases.

Effects on ability to drive or use machines
KYLEENA has no known influence on the ability to drive or use machine.

INTERACTIONS:
Interactions can occur with medicines that induce hepatic microsomal enzymes, which can result in increased clearance of sex hormones.

Substances increasing the clearance of levonorgestrel, e.g. Phenytoin, barbiturates, primidone, carbamazepine, rifampicin; 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 is not believed to be of major importance due to the local mechanism of action.

Substance with variable effects on the clearance of levonorgestrel, e.g.:
When co-administered with sex hormones, many HIV/HIC protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentration of levonorgestrel.

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 can be scanned safely by magnetic resonance imaging after placement of KYLEENA under the following conditions: Static magnetic field of 3-Tesla or less; spatial gradient field of 36000-Gauss/cm (360 T/m) or less; maximum whole body average specific absorption rate(SAR) of 4 W/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 to or less than 1,8 °C at a maximum whole body average specific absorption (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.

PREGNANCY AND LACTATION:
Pregnancy
The insertion of KYLEENA in pregnant women is contraindicated (see "Contraindications").

If the woman becomes pregnant when using KYLEENA, removal of the system is recommended since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labour. Removal of KYLEENA or probing of the uterus may result in spontaneous abortion. Ectopic pregnancy should be excluded. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, the woman 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.

Because of the intrauterine administration and local exposure to levonorgestrel, the possible occurrence of virilising effects in a female foetus should be taken into consideration. Clinical experience of the outcome of pregnancies under KYLEENA treatment is limited.

Lactation
In general, there appear to be no deleterious effects on infant growth or development when using any progestogen-only method after six weeks post-partum. KYLEENA does not affect the quantity or quality of breast milk. About 0,1 % of the levonorgestrel dose passes into the breast milk in nursing mothers.

Fertility
The use of LNG-IUS does not alter the course of future fertility. Upon removal of the LNG-IUS, women usually return to their normal fertility (see section "Pharmacodynamic properties").

DOSAGE AND DIRECTIONS FOR USE:
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. Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate a vasovagal reaction (e.g. syncope, or a seizure in an epileptic patient).

A woman should be re-examined four to twelve weeks after insertion and once a year thereafter, or more frequently if clinically indicated.
KYLEENA is not for use as a post-coital contraceptive.

Insertion and removal/replacement
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 and ultrasound examination.

KYLEENA can be identified by the combination of the visibility of the silver ring on ultrasound and the blue colour of the removal threads. The T- frame of KYLEENA contains barium sulphate which makes it visible in X-ray examination.

KYLEENA is removed by gently pulling on the thread with a 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 a narrow forceps. This may require dilatation of the cervical canal or surgical intervention.

KYLEENA should be removed no later than end of the fifth year. If the woman wishes to continue using the same method, a new KYLEENA 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 KYLEENA 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.

Insertion instructions
See separate enclosed insertion instruction leaflet.

Additional information on special populations
Paediatric patients
Safety and efficacy of KYLEENA have not been studied in women aged less than 18 years.

Geriatric patients
KYLEENA is not indicated for use 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 section "Contraindications").

Patients with renal impairment
KYLEENA has not been studied in women with renal impairment.

SIDE 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.
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.
The following bleeding patterns were observed in clinical trials with KYLEENA:

Bleeding patterns by 90-day reference period.

KYLEENA	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. amenorrhoea).

The frequencies of the side effects reported with KYLEENA are summarised in the table below.
Within each frequency grouping, side effects are presented in order of decreasing seriousness. The frequencies are crude incidences of the events observed in clinical trials in the indication contraception, including 1697 women and 5225, 52 women-years on KYLEENA.
Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000)

System organ class	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	Bleeding changes	Upper genital tract		**Uterine

system and breast disorders	including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea *Ovarian cyst Vulvovaginitis	infection dysmenorrhoea breast pain/discomfort Device expulsion (complete and partial) genital discharge		perforation

*Ovarian cysts had to be reported as side effects 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 section "Warnings and Special precautions").

Hypersensitivity including rash, urticaria and angioedema may occur.

Morphological changes of the endometrium and a weak local foreign body reaction were observed during use.

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 side effects 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 IUDs (including group A streptococcal sepsis) have been reported following insertion (see section "Warnings and Special precautions").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Not relevant.

IDENTIFICATION:
The product consists of an inserter and levonorgestrel intrauterine system, which is loaded at the tip of the inserter. Inserter has a grey flange. The system consists of drug reservoir mounted on a vertical stem of a T- body and covered with a semi-opaque membrane. The T- body has a loop at one end of the vertical stem and two arms at the other end. A silver ring is attached to the upper end of the vertical system. Blue removal threads are attached to the loop.

PRESENTATION:
The system, with the accessories, is packed in a thermoformed blister package (tray) and a peelable lid.

STORAGE INSTRUCTIONS:
Store at or below 30 °C. Keep out of reach of children.
The product is supplied in a sterile pack which should not be opened until required for insertion.
Each system is handled with aseptic precautions. If the seal of the sterile pack is broken, the system inside should be disposed of in accordance with the handling of bio-hazardous waste.
The Ghost IUD (essentially free of active ingredient; after use) and the inserter are disposed as biohazard material at the healthcare facility.

REGISTRATION NUMBER:
A 47/32.9/0037

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando, 1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:
Date on the registration certificate: 23 November 2017