MIRENA®

Intrauterine delivery system (IUS)

Important information, please read carefully!

Composition

Levonorgestrel 52 mg. The initial release rate is 20 micrograms /24 hours

Pharmacological Properties

Pharmacodynamic properties

Levonorgestrel is a progestin with anti-estrogenic activity used in gynecology in various ways: as the progestin component in hormone therapy and oral contraceptives and alone in the so-called 'minipills' and in subdermal implants. Mirena releases levonorgestrel directly into the uterus. This allows a very small daily dose, as the hormone is released directly into the target organ. The plasma concentrations of levonorgestrel are lower than with any other contraceptive method.

Mirena has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates endometrial estrogen and progesterone receptors, making the endometrium insensitive to the circulating estradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of Mirena. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the ovarian tubes inhibits sperm mobility and function, preventing fertilization. Ovulation is inhibited in some women.

The contraceptive efficacy of Mirena has been studied in 5 major clinical studies with 3330 women using Mirena. The failure rate (Pearl Index) was approximately 0.2 % at 1 year and the cumulative failure rate was approximately 0.7 % at 5 years. The failure rate also includes pregnancies due to undetected expulsions and perforations. Similar contraceptive efficacy has been observed in a large post-marketing study with more than 17000 women using Mirena. In a large prospective comparative non-interventional cohort study with an observation period of 1 year including more than 43.000 Mirena users, the Pearl Index of Mirena was 0.06 (95% CI: 0.04-0.09).
Because the use of Mirena 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 Mirena does not alter the course of the future fertility. About 80 % of the women wishing to become pregnant conceived within 12 months after removal of the system.

Mirena has been developed especially for women requiring long-term, effective contraception. Menorrhagia can also be effectively treated with Mirena. In menorrhagic women, the menstrual blood loss decreased by 62-94% at the end of three months and by 71- 95% at the end of six months of use. Compared to endometrial ablation or resection, Mirena demonstrated equal efficacy in reducing the menstrual blood loss up to two years. Reduced bleeding increases the hemoglobin level. Menorrhagia caused by submucosal myomas may not respond favourably to the treatment. Like oral contraceptive, Mirena also alleviates dysmenorrhea.

The effect of Mirena in the treatment of menorrhagia and in local progestin treatment in conjunction with estrogen replacement therapy is based on the action of levonorgestrel preventing proliferation of the endometrium. No cases of endometrial hyperplasia have been reported during a 12-month observation period. Prevention of proliferation has been equally good in patients administered estrogen orally, transdermally or subcutaneously. The amount of levonorgestrel released by Mirena is sufficient to prevent endometrial proliferation for five years. A sample should be taken from the uterus to check the endometrium before inserting a new Mirena in the uterine cavity, even if there has been no bleeding.

Pharmacokinetic properties

The active ingredient of Mirena is levonorgestrel. Levonorgestrel is directly released into the uterine cavity. Estimated *in vivo* release rates for different points in time are provided in table 1.

Table 1: Estimated *in vivo* release rates for Mirena:

Time	Estimated in vivo release rate [µg/24 hours]
Initial	20
1 year after insertion	18
5 years after insertion	10
Average over 5 years	15

MIRENA/Levonorgestrel/Intrauterine system-IUS/BEC 11189 CCDS #19, BEC 9232, BPOM deficiency letter 13.11.2020

DISETUJUI OLEH BPOM : 23/11/2020 ID REG : EREG10036611900161

Absorption
Following insertion, levonorgestrel is released into the uterine cavity without delay based on serum concentration measurements. More than 90% of the released levonorgestrel is systemically available.

After insertion of Mirena, levonorgestrel is detectable in serum after 1 hour. The maximum concentration is reached within 2 weeks after insertion. In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 pg/ml (25th to 75th percentiles: 151 pg/ml to 264 pg/ml) at 6 months to 194 pg/ml (146 pg/ml to 266 pg/ml) at 12 months, and to 131 pg/ml (113 pg/ml to 161 pg/ml) at 60 months in women of reproductive age weighing above 55 kg.

The high local drug exposure in the uterine cavity, leads to a strong concentration gradient via 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).

In postmenopausal women using Mirena together with non-oral estrogen treatment, the median serum concentration of levonorgestrel declines from 257 pg/ml (25th to 75th percentiles: 186 pg/ml to 326 pg/ml) at 12 months to 149 pg/ml (122 pg/ml to 180 pg/ml) at 60 months.When Mirena is used together with oral estrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approx. 478 pg/ml (25th to 75th percentiles: 341 pg/ml to 655 pg/ml) due to the induction of the Sex hormone-binding globulin (SHBG) by oral estrogen treatment.

Distribution
Levonorgestrel is bound non-specifically to serum albumin and specifically to the Sex hormone-binding globulin (SHBG). 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. The concentration of SHBG declined on average by about 20-30% during the first month after insertion of Mirena, remained stable during the first year and increased slightly thereafter. The mean apparent volume of distribution of levonorgestrel is about 106 L.

Body weight and serum SHBG concentration have been shown to affect systemic levonorgestrel concentration i.e. low body weight and/or a high SHBG level increase levonorgestrel concentration. In women of reproductive age with a low body weight (37 to 55 kg) the median serum concentration of levonorgestrel is about 1.5-fold higher.

Biotransformation
Levonorgestrel is extensively metabolized. 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 LNG. The available *in vitro* data suggest that CYP mediated biotransformation reactions may be of minor relevance for LNG 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 with the feces and urine at an excretion ratio of about 1. The excretion half-life which is mainly represented by metabolites, is about 1 day.

Linearity / non-linearity
The pharmacokinetics of levonorgestrel is 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 local action of Mirena, no impact on the efficacy of Mirena is expected.

Preclinical safety data

The preclinical safety evaluation revealed no special hazard for humans based on studies of safety pharmacology, pharmacokinetics, toxicity, genotoxicity, and carcinogenic potential of levonorgestrel. Levonorgestrel is a widely-used progestin. The safety profile following systemic administration is well documented. Studies in monkeys with intrauterine delivery of levonorgestrel for 9 to 12 months confirmed local pharmacological activity with good tolerance and no signs of systemic toxicity. No embryotoxicity was seen in a study in rabbits.

Indications

- Contraception,
- Idiopathic menorrhagia,
- Protection from endometrial hyperplasia during estrogen replacement therapy.

Dosage and method of administration

Method of administration

Mirena is inserted into the uterine cavity and is effective for five years

The in vivo dissolution rate is approximately 20 µg/24 hours initially and is reduced to approximately 18 µg/24 hours after 1 year and to 10 µg/24 hours after five years. The mean dissolution rate of levonorgestrel is about 15 µg/24 hours over the time up to five years.

Insertion and removal/replacement

Use of Mirena as a contraceptive: In women of fertile age, Mirena is to be inserted into the uterine cavity within seven days of the onset of menstruation. Mirena can be replaced by a new system at any time in the cycle. The system 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, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

Mirena is not recommended as the contraceptive method of first choice for young women who have never given birth.
The system should be removed after five years. If the user wishes to continue using the same method, a new system can be inserted at the same time.

If pregnancy is not desired, the removal should be carried out within 7 days of the onset of menstruation in women of fertile age, provided the woman is 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 a risk of pregnancy. To ensure continuous contraception a new system should be immediately inserted or an alternative contraceptive method should have been initiated.

Mirena in the treatment of idiopathic menorrhagia: In women of fertile age, Mirena is to be inserted into the uterine cavity within seven days of the onset of menstruation. Mirena can be replaced by a new system at any time in the cycle.

Mirena as a local progestin treatment in conjunction with estrogen replacement therapy: A sample should be taken from the uterine cavity to check the endometrium before insertion of Mirena because spotting is common during the first months of therapy. Mirena can be inserted at any time in an amenorrheic woman, or during the last days of menstruation or withdrawal bleeding. New specimens are not usually required during the 12 months following insertion. Vaginal ultrasonography is recommended 12 months after insertion. An endometrial sample should be taken if the endometrium is thicker than 5 mm or the patient has had extra bleedings. In the treatment of menorrhagia and in local progestin treatment in conjunction with estrogen replacement therapy Mirena releases a sufficient amount of levonorgestrel during a five-year period to prevent proliferation of the endometrium. A sample should be taken from the uterus to check the endometrium before insertion of a new Mirena, even if there has been no bleeding.

It is recommended that Mirena should only be inserted by physicians/health care professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion.

Mirena is removed by gently pulling on the threads with a forceps. If the threads are not visible and the system is in the uterine cavity, it may be removed using a narrow tenaculum. This may require dilatation of the cervical canal or other surgical intervention.

Mirena, 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 0.7% at 5 years.

After removal of Mirena, the system should be checked to be intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

Instruction for use and handling and disposal:

Mirena is supplied in a sterile pack which should not be opened until required for insertion.
The exposed product should be handled with aseptic precautions. If the seam of the sterile package is broken, the product should be discarded. Detailed instructions for insertion are in the package.

Additional information on special populations

Geriatric patients
Mirena has not been studied in women over the age of 65 years.

Patients with hepatic impairment
Mirena is contraindicated in women with acute liver disease or liver tumor (see Contraindications).

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

Pediatric population
Use of this product before menarche is not indicated.

Contraindications

Known or suspected pregnancy;
Current or recurrent pelvic inflammatory disease;
Lower genital tract infection;
Postpartum endometritis;
Infected abortion during the past three months;
Cervicitis;
Cervical dysplasia;
Uterine or cervical malignancy;
Progestogen-dependent tumors;
Undiagnosed abnormal uterine bleeding;
Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity;
Conditions associated with increased susceptibility to infections;
Acute liver disease or liver tumor;
Thromboembolic process;
Hypersensitivity to the active substance or to any of the excipients

Special warnings and special precautions for use

Mirena may be used with caution after specialist consultation, or removal of the system should be considered if the patient experiences for the first time migraine, exceptionally severe headache, jaundice or marked increase in blood pressure, confirmed or suspected hormone dependent cancer, including breast cancer or if the patient is diagnosed with malignant hematological disease or leukemia, severe arterial disease such as stroke or myocardial infarction, or thrombophlebitis.

Glucose tolerance may be affected with Mirena in place and, therefore, the blood glucose concentration should be monitored in diabetics. However, there is generally no need to alter the therapeutic regimen in diabetics using Mirena. Irregular bleedings may mask symptoms of cervical or endometrial cancer. For this reason, the physician must ensure before insertion of Mirena that the patient has had a cervical smear, which should be normal, during the three months preceding the insertion. A uterine sample should be normal in conjunction with estrogen replacement therapy. Bleeding irregularities developing with Mirena in place should be investigated as described above at the discretion of the physician.

Mirena is not the method of first choice for postmenopausal women with advanced uterine atrophy.

Due to the limited exposure in Mirena trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy, the available data are not sufficient to confirm or refute a risk for breast cancer when Mirena is used in this indication.

Medical examination/consultation

Before insertion, the woman must be informed of the efficacy, risks and side effects of Mirena. A physical examination including pelvic examination, and examination of the breasts, should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional´s evaluation. Pregnancy and sexually transmitted diseases should be excluded, and genital infections have to be successfully treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of Mirena is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximize efficacy. Therefore, the instructions for the insertion should be followed carefully. Because the insertion technique is different from other intrauterine devices, special emphasis should be given to training in the correct insertion technique. 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 women should be re examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

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

Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of Mirena.

If the woman continues the use of Mirena inserted earlier for contraception, endometrial pathology has to be excluded in case bleeding disturbances appear after commencing estrogen replacement therapy.

If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken.

Oligomenorrhea and amenorrhea

In women of fertile age, oligomenorrhea and amenorrhea develops gradually in 57% and 16% of women during the first year of use, respectively. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation and a check should be made to ensure that the system is still in place.

Amenorrhea is an effect that can be positive for some and negative for others. In clinical studies, the discontinuation rate for amenorrhea during the first year of use was 1.7%. Due to the strong local effect of levonorgestrel on the endometrium, the endometrial lining does not react to estrogen and, therefore, proliferation does not occur. The duration and volume of menstrual bleeding is reduced. When women with different patterns were compared, no clear difference in follicle development, ovulation or estradiol or progesterone production was found. During the first three months, the volume of menstrual bleeding decreased by 88% in menorrhagic women. Reduced bleeding increased the hemoglobin level.
Over a 12-month observation period, amenorrhea developed in more than 50% of users during local progestin treatment in conjunction with estrogen replacement therapy. Irregular bleeding and spotting were fairly common during the first three months of use.

Pelvic infections

The insertion tube helps to protect Mirena from contamination with micro-organisms during the insertion. On the basis of experience obtained from users of copper intrauterine devices, the risk of infection is greatest during the first month of use, after which the rate of infections decreases. The risk of infection is highest in young women or if the woman or her partner have multiple sexual partners. Pelvic infection may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUD insertion, although this is extremely rare.

If an acute infection does not respond to treatment within a few days, or if the woman experiences recurrent endometritis or other pelvic infection, Mirena must be removed. Some studies indicate that the rate of pelvic infections in users of Mirena is lower than in users of copper intrauterine devices.

Expulsion

Mirena may be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. Symptoms of the partial or complete expulsion of the IUS may include bleeding and pain. However, the system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. Partial expulsion may decrease the effectiveness of Mirena. As Mirena normally decreases menstrual flow, increase of bleeding may be indicative of an expulsion

A displaced Mirena should be removed. A new system can be inserted at that time.

The woman should be advised how to check the threads of Mirena.

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 some time later and may decrease the effectiveness of Mirena. Such a system must be removed.

In a large prospective comparative non-interventional cohort study in IUD users (N = 61,448 women) with a 1-year observational period, 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 Mirena cohort and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women using Mirena or copper IUD), the incidence of perforation detected at any time during the entire 5-year period was 2.0 (95% CI: 1.6 – 2.5) per 1000 insertions.

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 2). These risk factors were confirmed in the subgroup followed up for 5 years. Both risk factors were independent of the type of IUD inserted.

Table 2: Incidence of perforation per 1000 insertions for the entire study cohort observed over 1 year, 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=6047 insertions)	1.7 (95% CI 0.8-3.1; n=5927 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=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 amenorrheic woman starts bleeding. In clinical trials the ectopic pregnancy rate with Mirena was approximately 0.1% per year. In a large prospective comparative non-interventional cohort study with an observation period of 1 year, the ectopic pregnancy rate with Mirena was 0.02%. This rate is lower than in women not using any contraception (0.3-0.5% per year). The absolute risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in situ, the relative likelihood of ectopic pregnancy is increased.

Lost threads

If the retrieval 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 with a suitable instrument. If they cannot be found, the possibility of expulsion or perforation should be considered. Ultrasound diagnosis may be used to ascertain the correct position of the system. If ultrasound is not available or successful, X-ray may be used to locate Mirena.

Ovarian cysts

Since the contraceptive effect of Mirena is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. Ovarian cysts have been reported as adverse drug reactions in approximately 7% of women using Mirena. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases, the ovarian cysts disappear spontaneously during two to three months observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

Fertility, pregnancy and lactation

Pregnancy

The use of Mirena during an existing or suspected pregnancy is contraindicated (see Contraindications).

If the woman becomes pregnant when using Mirena removal of the system is recommended, since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labor. Removal of Mirena 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, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should also 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 the local exposure to the hormone, the possible occurrence of virilizing effects in the fetus should be taken into consideration. Clinical experience of the outcomes of pregnancies under Mirena is limited due to the high contraceptive efficacy, but the woman should be informed that, to date, there is no evidence of birth defects caused by Mirena use in cases where pregnancy continues to term with Mirena in place

Lactation

About 0.1 % of the levonorgestrel dose is transferred to the infant during breast-feeding. However, it is not likely that there will be a risk for the infant with the dose released from Mirena, when it is inserted in the uterine cavity. There appears to be no deleterious effect on infant growth or development when using Mirena after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk. Uterine bleeding has rarely been reported in women using Mirena during lactation.

Fertility

Upon removal of Mirena, women return to their normal fertility.

Effects on ability to drive and use machines

Not known.

Undesirable effects

Summary of the safety profile

The majority of women experience changes in menstrual bleeding pattern after insertion of Mirena. During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after postmenstrual insertion of Mirena, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, amenorrhea is experienced by 0% and infrequent bleeding by 11% during the first 90 days, increasing to 16% and 57% at the end of the first year of use, respectively.

When Mirena is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with Mirena are summarized in the table below. 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) and unknown. 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 in the indications contraception and idiopathic menorrhagia/ heavy menstrual bleeding, including 5091 women and 12,101 woman-years.

Adverse reactions in clinical trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy (including 514 women and 1218.9 woman-years) were observed at a similar frequency unless specified by footnotes.

Table 3: adverse drug reactions

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
Immune system disorders					Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders		Depressed mood/ Depression			
Nervous system disorders	Headache	Migraine			
Gastrointestinal disorders	Abdominal/pelvic pain	Nausea			
Skin and subcutaneous tissue disorders		Acne Hirsutism	Alopecia		
Musculosceletal, connective tissue and bone disorders		Back pain**			
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst Dysmenorrhea Breast pain** Intra-uterine contraceptive device expelled (complete and partial)	Uterine perforation***		
Investigations					Blood pressure increased

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

*Endometrial protection trials: “common”

** Endometrial protection trials: “very common”

*** This frequency is based on a large prospective comparative non-interventional cohort study in IUD users which showed that breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth are independent risk factors for perforation, (see section ‘Special warnings and precautions for use’). In clinical trials with Mirena that excluded breastfeeding women the frequency of perforation was "rare".

Pregnancy, puerperium and perinatal conditions:
When a woman becomes pregnant with Mirena in situ, the relative risk of ectopic pregnancy is increased.

Reproductive system disorders:
The removal threads may be felt by the partner during intercourse.

Breast disorders:
The risk of breast cancer is unknown when Mirena is used in the indication protection from endometrial hyperplasia during estrogen replacement therapy. Cases of breast cancer have been reported (frequency unknown, see Section Special warnings and special precautions of use).

Injury, poisoning and procedural complications:

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

Infections and Infestations:
Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section special warnings and precautions for use).

Interaction with other medicaments and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effects of other medicinal products on Mirena
Interactions can occur with drugs that induce or inhibit microsomal enzymes, which can result in increased or decreased 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 drugs on the contraceptive efficacy of Mirena 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:
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 progestin.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors), e.g.:
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 progestin.

Storage

Store below 30ºC

Presentation

Box @ 1 IUS
Reg. No.: XXXXX

Harus dengan resep dokter

Manufactured by:

Bayer Oy,
Turku-Finland

Imported by:
PT. Bayer Indonesia,
Depok-Indonesia