



SELECT THE REQUIRED INFORMATION



PROFESSIONAL INFORMATION



PATIENT INFORMATION LEAFLET

APPLICANT: BAYER (Pty) Ltd
PRODUCT NAME: MIRENA
DOSAGE FORM(S): INTRA-UTERINE DELIVERY SYSTEM
STRENGTH(S): 20 µg/ 24 hour

APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

MIRENA

Intrauterine delivery system

COMPOSITION:

Active: Levonorgestrel intrauterine system 20 µg/ 24 hours. Each sterile intrauterine system contains levonorgestrel 52 mg.

Inactives: barium sulphate, colloidal anhydrous, iron oxide, polydimethylsiloxane elastomer, silica and polyethylene.

PHARMACOLOGICAL CLASSIFICATION:

A. 34. Other

Pharmacodynamic properties:

Levonorgestrel is a progestogen with anti-oestrogenic activity.

Levonorgestrel intrauterine system has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentrations in the endometrium down-regulate oestrogen 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 the levonorgestrel intrauterine system.

Thickening of the cervical mucous 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 fertilisation. Ovulation is inhibited in some women.

Pharmacokinetic properties:

Absorption:

Following insertion, the levonorgestrel intrauterine system (52 mg) releases levonorgestrel. The *in vivo* release rate of levonorgestrel in uterine cavity is initially approximately 20 µg/ 24 hours and declines to 10 µg/ hours after 5 years.

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Distribution:

Levonorgestrel is bound non-specifically to serum albumin and specifically to Sex Binding Human Globulin (SHBG). About 1 to 2 % of the circulating levonorgestrel is present as free steroid and 42 to 62 % is specifically bound to SHBG. During the use of levonorgestrel intrauterine system, the concentration of SHBG declines. Accordingly, the fraction bound to SHBG decreases during the treatment and the free fraction increase. The mean apparent volume of distribution of levonorgestrel is about 106 litres. Due to a 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.

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.

In postmenopausal women using levonorgestrel intrauterine system together with non-oral oestrogen 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 levonorgestrel intrauterine system is used together with oral oestrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approximately 478 pg/ ml (25th to 75th percentile 341 pg/ ml to 655 pg/ ml) due to induction of SHBG by oral oestrogen treatment.

Biotransformation:

Levonorgestrel is extensively metabolised. The major metabolites in the plasma are unconjugated and conjugated forms of 3 α , 5 β -tetrahydrolevonorgestrel. Based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel, CYP2E1, CYP2C19 and CYP2C9 may also be involved , but to a lesser extent.

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 faeces and urine at an excretion ratio of about 1. The excretion half-life which is mainly represented by the metabolites, is about 1 day

INDICATIONS:

Contraception.
Idiopathic menorrhagia.

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Protection from endometrial hyperplasia during oestrogen replacement therapy.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.
Known or suspected pregnancy (see Pregnancy and Lactation);
Current or recurrent pelvic inflammatory disease;
Lower genital tract infection;
Postpartum endometritis;
Septic (infected) abortion during the past three months;
Cervicitis;
Cervical dysplasia;
Uterine or cervical malignancy;
Undiagnosed abnormal uterine bleeding;
Progestogen-dependent tumours;
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 tumour.

WARNINGS AND SPECIAL PRECAUTIONS:

Mirena should be used with caution and only after specialist consultation; alternatively, 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;
- severe headache;
- jaundice;
- marked increase of blood pressure;
- severe arterial disease such as stroke or myocardial infarction.

There is no consensus about the possible role of progestogens, as in Mirena, in patients with varicose veins and superficial thrombophlebitis in the causation of venous thromboembolism.

Mirena should be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. Antibiotic prophylaxis should be administered to these women when inserting or removing the intrauterine delivery system.

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

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The available data are not sufficient to confirm or refute a risk for breast cancer when Mirena is used in the indication protection from endometrial hyperplasia during oestrogen replacement therapy.

Oligo/amenorrhoea:

In women of fertile age, oligomenorrhoea and amenorrhoea develops in 57 % and 16 % of women respectively. The possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the onset of previous menstruation. A repeated pregnancy test is not necessary in amenorrhoea subjects unless indicated by other signs of pregnancy.

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

Pelvic infection:

The insertion tube helps to reduce contamination of Mirena with micro-organisms during the insertion. The highest rate of pelvic infections occurs during the first month after insertion and decreases later.

Severe infections or sepsis (including group A streptococcal sepsis) can occur following IUD insertion such as Mirena,

If the woman experiences recurrent endometritis or pelvic infections or if an acute infection is severe or does not respond to treatment within a few days, Mirena must be removed.

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

Expulsion:

Symptoms of the partial or complete expulsion of Mirena may include bleeding or 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 decreases menstrual flow, increase of menstrual flow 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 Mirena may occur, most often during insertion, and may decrease the effectiveness of Mirena. If this occurs Mirena must be removed.

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In a large European prospective comparative non-interventional cohort study in IUD users (N = 61448 women), the incidence perforation was 1,3 (95 % CI: 1,1 to 1,6) per 1000 insertions. 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 1).

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 = 41 910 insertions)

The risk of perforations 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. 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 to 0,5 % per year). 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

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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. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Ovarian cysts have been reported as adverse drug reactions in approximately 7 % of women using Mirena. Most of these cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

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

Effects on ability to drive and use machines:

Not known

INTERACTIONS:

The metabolism of progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, and carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

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

PREGNANCY AND LACTATION:

Pregnancy:

The use of Mirena during an existing or suspected pregnancy is contra indicated (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 labour. Removal of Mirena or probing of the uterus may result in spontaneous abortion. If the intrauterine contraceptive cannot be gently removed, termination of pregnancy may be considered. 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.

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Ectopic pregnancy should be excluded. 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 virilising effects in the foetus should be taken into consideration.

Lactation:

About 0.1 % levonorgestrel dose is transferred to the infant during breastfeeding. Progestogen-only methods do not appear to affect the quantity or quality of breast milk.

Non-hormonal contraceptive methods/devices are the methods of choice during lactation. However, if progestogen only contraception is judged as appropriate for lactating women, Mirena may be used.

Uterine bleeding has been reported in women using Mirena during lactation.

Fertility:

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

DOSAGE AND DIRECTIONS FOR USE:

One unit is inserted into the uterine cavity. One administration is effective for five years. The *in vivo* dissolution rate is about 20 µg/ 24 hours initially and is reduced to about 11 µg/ 24 hours after five years. The mean dissolution rate of levonorgestrel is about 14 µg/ 24 hours over the time up to five years.

In women under hormonal replacement therapy, Mirena can be used in combination with oral or transdermal oestrogen preparations without progestogens.

Mirena, when inserted according to the insertion instructions, has a failure rate of approximately 0,2 % at 1 year and accumulative failure rate of approximately 0,7 % at 5 years. The failure rate may increase in case of expulsion or perforation.

Additional information on special population:

Children and adolescents:

Safety and efficacy of Mirena have been established in women of reproductive age. There is no relevant indication for the use of Mirena before menarche.

Geriatric patients:

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

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Patients with hepatic impairment:

Mirena is contraindicated in women with acute liver disease or liver tumour (see section on CONTRAINDICATIONS).

Patients with renal impairment:

Mirena has not been studied in women with renal impairment.

Instructions for use/handling:

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. Special instructions for insertion are in the package.

Because the insertion technique is different from other intrauterine devices, special emphasis should be given to training in the correct insertion technique.

Any unused product or waste material should be disposed of in accordance with local requirements.

Insertion and removal/replacement:

Before insertion, the woman must be informed of the efficacy, risks and side effects of Mirena. A physical examination including pelvic examination, examination of the breasts, and a cervical smear should be performed. 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 maximise efficacy. Therefore, the instructions for the insertion should be followed carefully. The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated. 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 insertion should be delayed until the uterus is involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. It is recommended that Mirena should only be inserted by medical practitioners/ healthcare professionals who are experienced in Mirena insertion and/ or have undergone sufficient training for Mirena insertion. In case of a difficult insertion, physical examination and ultrasound should be performed immediately to exclude perforation.

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

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When used for endometrial protection during oestrogen replacement therapy, Mirena can be inserted at any time in an amenorrhoeic woman, or during the last days of menstruation or withdrawal bleeding.

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 oestrogen replacement therapy.

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

Mirena is removed by gently pulling on the threads with 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. If dilation is required, consider using analgesics and/or a paracervical block. 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 during the menstruation in women of fertile age, provided that there appears to be a menstrual cycle. Otherwise contraception has to be ensured with other methods (e.g. condoms) starting at least 7 days before the removal. When the woman has no menses, she should also use barrier methods of contraception starting seven days before removal and has to continue with this until her menstruation reappears.

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 Mirena has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

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 woman.

Insertion instructions:

See separate enclosed insertion instruction leaflet.

Important:

Should you suspect that the system is not in the correct position, remove it and insert a new one.

Removal of Mirena:

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Mirena can be removed by pulling the removal threads with 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. Unless a pregnancy is desired, the system should not be removed after the fifth day of the menstrual cycle in a sexually active woman.

SIDE EFFECTS:

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. Amenorrhoea increases from 0 % to 16 % and infrequent bleeding increases from 11 % to 57 % from the first 90 days until the end of the first year of use respectively.

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

Adverse events reported in clinical studies:

The adverse drug reaction frequencies were observed in the clinical trials in the indication 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 oestrogen replacement therapy (including 514 women and 1218,9 woman-years) were observed at a similar frequency unless specified by footnotes.

System Organ Class	Very Common ≥1/ 10	Common ≥ 1/100, < 1/10	Uncommon ≥ 1/1000, < 1/100	Rare ≥ 1/10000, <1/1000	Unknown
Immune system disorder					Hypersensitivity including rash, urticaria and angiodema.
Psychiatric disorders		Depressed mood/ Depression			

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Nervous system disorders	Headache	Migraine			
Gastrointestinal disorders	Abdominal/ pelvic pain	Nausea			
Skin and subcutaneous tissue disorders		Acne Hirsutism	Alopecia		
Musculoskeletal 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, Dysmenorrhoea, breast pain**, Intra-uterine contraceptive device expelled (complete and partial)		Uterine perforation***	
Investigations				Blood pressure increased	

* Endometrial protection trials: "common"

** Endometrial protection trials: "very common"

*** In a large prospective comparative non-interventional cohort study in IUD users, the frequency of perforation in women who were breastfeeding or had insertions up to 36 weeks after delivery was increased (frequency – "uncommon") (see WARNINGS AND SPECIAL PRECAUTIONS).

When a woman becomes pregnant with Mirena in situ, the relative risk of ectopic pregnancy is increased.

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

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The risk of breast cancer is unknown when Mirena is used in the indication protection from endometrial hyperplasia during oestrogen replacement therapy.

Cases of breast cancer have been reported (frequency unknown, see WARNINGS AND SPECIAL PRECAUTIONS).

Injury, poisoning and procedural complications:

The following adverse drug reactions 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 epileptic patients.

Infections and infestations:

Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see WARNINGS AND SPECIAL PRECAUTIONS).

Postmarketing side effects:

The following adverse reactions have been identified during post approval use of Mirena:

Immune system disorders: Hypersensitivity including rash, urticarial and angioedema

Investigations: Blood pressure increased

Infections and infestations: Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see WARNINGS AND SPECIAL PRECAUTIONS).

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to the medicine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Not relevant

IDENTIFICATION:

The levonorgestrel intrauterine delivery system consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end.

Removal threads are attached to the loop. The vertical stem of the intrauterine delivery system is loaded in the insertion tube at the tip of the inserter. The intrauterine delivery system and inserter are essentially free of visible impurities.

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PRESENTATION:

The system, with the accessories, is packed into a heat sealed sterilization pouch.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from moisture and direct sunlight. Keep out of reach of children.

REGISTRATION NUMBER:

A 32/34/0332

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Reg No.: 1968/011192/ 07
27 Wrench Road
Isando

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of the registration certificate of the medicines:

26/02/1999

Date of most recently revised package insert as approved by Council:

05 JUNE 2019

BOTSWANA: BOT0700957 S2
MAURITIUS: R9846/ 02/14
NAMIBIA: 04/34/1017 S2

Updated information of the Professional Information for this medicine is available by scanning the QR code included in the package leaflet and/or outer carton with a smartphone. The same information is also available on the following URL:

https://www.bayer.co.za/static/documents/MSDS/Pis/MIRENA_EN_PI.pdf