

PRODUCT MONOGRAPH

Pr **MIRENA**[®]

Levonorgestrel-releasing Intrauterine System (52 mg) to deliver
up to 20 µg levonorgestrel per day

Progestogen

Berlex Canada Inc.
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Pr **MIRENA**[®]

Levonorgestrel-releasing Intrauterine System

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intra-uterine	Intrauterine system / 52 mg levonorgestrel	barium sulphate, iron oxide, polydimethylsiloxane, polyethylene, silica <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

MIRENA (levonorgestrel-releasing intrauterine system) is indicated for: conception control

CONTRAINDICATIONS

MIRENA (levonorgestrel-releasing intrauterine system) is contraindicated in patients with the following conditions:

- known or suspected pregnancy
- current or recurrent pelvic inflammatory disease
- lower genital tract infection
- postpartum endometritis
- undiagnosed abnormal uterine bleeding
- uterine anomalies including fibroids if they distort the uterine cavity
- uterine or cervical malignancy
- cervicitis
- cervical dysplasia
- acute liver disease or liver tumour
- septic abortion within the previous three months
- hypersensitivity to levonorgestrel or any of the other ingredients in the formulation or component of the container components of MIRENA. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- bacterial endocarditis
- established immunodeficiency
- acute malignancies affecting blood or leukemias
- recent trophoblastic disease while hCG levels are elevated

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Patients should be counseled that MIRENA (levonorgestrel-releasing intrauterine system) does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs). For protection against STDs, patients should be counseled to use latex condoms.

General

MIRENA should be used with caution in women who have migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia, severe headache, marked increase in blood pressure or confirmed or suspected hormone dependent neoplasia including breast cancer, or active or previous severe arterial disease such as stroke or myocardial infarction. Removal of MIRENA should be considered if any of the above conditions occur during use.

MIRENA is not the contraceptive method of first choice for young, nulligravid women. Controlled clinical trials were done in previously parous women aged mainly over 18 years.

MIRENA is intended for use in women of child-bearing age.

The effects of MIRENA on the ability to drive and use machines have not been studied.

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

Cardiovascular

MIRENA should be used with caution in women with congenital or valvular heart disease who are at risk of infective endocarditis. Antibiotic prophylaxis should be administered to such patients when inserting or removing MIRENA.

Endocrine and Metabolism

Glucose Tolerance

Combination and progestogen-only oral contraceptives, including those containing levonorgestrel, may affect glucose tolerance in some users. Diabetic patients, and those with a family history of diabetes, should be observed closely to detect any alterations in carbohydrate metabolism. Young diabetic patients whose disease is of recent origin, well-controlled and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be closely observed.

Genitourinary

Bleeding irregularities

Because irregular menstrual bleeding or spotting is common during the first few months of use, endometrial pathology should be excluded prior to insertion of MIRENA. Irregular bleeding patterns in users of MIRENA could mask the signs and symptoms of cervical or endometrial cancer. If bleeding irregularities develop after prolonged use, appropriate diagnostic measures should be undertaken.

Prolonged menstrual bleeding may occur during the first few months, however with continued use, bleeding patterns vary from regular scanty menstruation in some women to oligomenorrhea or amenorrhea in others. Oligomenorrhea or amenorrhea develop gradually in about 20% of users. Reduced bleeding increases the level of blood hemoglobin.

The possibility of pregnancy should be considered if menstruation does not occur after six weeks or more of amenorrhea, following a pattern of regular menses. A pregnancy test is not necessary in amenorrheic women unless indicated by other symptoms.

Hematologic

Thromboembolism

Epidemiological studies have indicated that women using progestogen-only oral contraceptives may have a slightly increased risk of venous thromboembolism; however, the results are not statistically significant. Appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms or signs of thrombosis in users of MIRENA. Symptoms of thromboembolism include: unilateral leg pain and/or swelling, sudden severe pain in the chest whether or not it radiates to the left arm, sudden breathlessness, sudden onset of coughing, any unusual severe prolonged headache, sudden partial or complete loss of vision, diplopia, slurred speech or aphasia, vertigo, collapse with or without focal seizure, weakness or very marked

numbness suddenly affecting one side or part of the body, motor disturbances and acute abdomen. Symptoms or signs of retinal thrombosis are: unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

Hepatic/Biliary/Pancreatic

If jaundice develops in a patient using MIRENA, consideration should be given to removing the system. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Sexual Function/Reproduction

Ovarian Cysts (Delayed Follicular Atresia)

Since the contraceptive action of MIRENA is due mainly to its local effect on the uterus, 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.

Enlarged follicles were diagnosed in about 12% of women using MIRENA in one study involving 50 women. In a larger clinical trial (n=2,246), the rate of functional ovarian cysts was 1.2 per 100 woman-years. Cysts are usually small and disappear spontaneously within a few months.

Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the enlarged follicles disappear spontaneously over a two to three month period. Should this not occur, continued ultrasound monitoring and other diagnostic or therapeutic measures are recommended. Rarely, surgical intervention may be required.

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 association with missed periods.

Ectopic pregnancies with MIRENA are very rare. In one clinical trial with 1,821 women using MIRENA, the reported rate of ectopic pregnancy was 0.02 per 100 woman-years. This rate is significantly lower than the estimated rate of 1.2 to 1.6 for women using no contraceptive method.

Combined data from prospective clinical trials with MIRENA reveal an overall rate of ectopic pregnancy of 0.06 per 100 woman-years. A post-marketing surveillance study with data from over 17,000 women using MIRENA also indicated an ectopic pregnancy rate of 0.08 per 100 woman-years.

Pelvic Infection

The inserter provided with MIRENA helps protect the system from contamination with microorganisms during insertion, thereby minimizing the risk of pelvic infection. Known risk factors for pelvic inflammatory disease include multiple sexual partners, frequent intercourse and young age.

If recurrent endometritis or pelvic infections are experienced, or if an acute infection does not

respond to treatment within a few days, MIRENA must be removed.

Perforation

Perforation or penetration of the uterus or cervix is rare (occurring at a rate of between 1/1,000 and 1/10,000), most often occurring during insertion. MIRENA should be removed as soon as possible if this occurs. The number of uterine perforations is linked to the experience of the person inserting the system⁵. To reduce the possibility of perforation, it is important to follow the recommended insertion technique. (See **Post-market Adverse Drug Reactions and Dosage and Administration: Insertion Instructions.**)

Sexually Transmitted Diseases

Patients should be counseled that MIRENA does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs). For protection against STDs, patients should be counseled to use latex condoms.

Ophthalmologic

Contact Lenses

Visual changes or changes in contact lens tolerance may occur in users of MIRENA. If this occurs an ophthalmologist should be consulted.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while using MIRENA. In cases of a serious recurrence, consideration should be given to removing MIRENA since the depression may be drug-related.

Special Populations

Pregnant Women: MIRENA is not to be used during an existing or suspected pregnancy. If a patient becomes pregnant while using MIRENA, removal of the system is recommended since any intrauterine system left in place may increase the risk of abortion and preterm labour. Removal of MIRENA or probing of the uterus may result in spontaneous abortion. If the system cannot be gently removed, termination of the pregnancy may be considered. If the patient wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks to the infant of premature birth. The course of such a pregnancy should be closely monitored. Ectopic pregnancy should be excluded. The patient should be instructed to report all symptoms that suggest complications of the pregnancy, such as cramping abdominal pain with fever.

Because of the local exposure of the fetus to levonorgestrel, teratogenicity (especially virilization) cannot be completely excluded.

Due to the high contraceptive efficacy of MIRENA, clinical experience with MIRENA during full term pregnancy is limited. However, the patient should be informed that there is no evidence of birth defects associated with MIRENA in cases where pregnancy has continued to term with the system in place.

Nursing Women: Hormonal contraceptives are not recommended as the contraceptive method of first choice in breast-feeding women. Although levonorgestrel has been found in the breast milk of women using MIRENA, there does not appear to be a detrimental effect on growth or development of breast-fed infants whose mothers started using the product after six weeks postpartum. Progestogen-only contraceptive methods do not appear to affect the quantity and quality of breast milk.

Pediatrics (< 18 years of age): MIRENA is not the contraceptive method of first choice for young, nulligravid women. Controlled clinical trials were done in previously parous women aged mainly over 18 years.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly occurring adverse events (i.e., in greater than 10% of users) that are observed postmarketing include menstrual bleeding changes and benign ovarian cysts.

Different kinds of bleeding changes (frequent, prolonged or heavy bleeding, spotting, oligomenorrhea, amenorrhea) are experienced by all users of MIRENA (levonorgestrel-releasing intrauterine system).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical studies, the most common adverse event occurring with MIRENA is a change in menstrual bleeding patterns (see **Action and Clinical Pharmacology**). The changes may include spotting, shorter or longer menstrual periods, irregular bleeding, oligomenorrhea, amenorrhea, heavy flow, back pain and dysmenorrhea.

In one large clinical trial with MIRENA, the gross cumulative removal rate for bleeding was 13.7 per 100 women at five years. During the first year after insertion, 16.8% of MIRENA users experienced an interval of amenorrhea lasting at least 90 days. The cumulative net removal rate for amenorrhea was 4.3 per 100 women, with removals for this reason more frequent among younger women than older women.

Ectopic pregnancy has been reported with MIRENA. Pelvic inflammatory disease may also occur. The system or parts of it may perforate the uterine wall, but this is very rare. Enlarged follicles (functional ovarian cysts) may develop.

Adverse events are most common during the first months after insertion of MIRENA; their frequency subsides subsequently. In clinical trials, reported conditions elicited by non-specific

questioning in 2,213 women at three months and in 902 women at sixty months after insertion of MIRENA, are listed in the following table:

Table 1: Adverse events reported in MIRENA clinical trials occurring at a rate of more than 1%

Reported adverse event	Incidence (%)	
	After 3 Months (n=2,213)	After 60 Months (n=902)
<u>Infections and infestations:</u>		
upper respiratory tract infection	0.9	1.7
sinusitis	0.6	1.0
candidiasis	0.5	1.2
bronchitis	0.2	1.8
urinary tract infection	0.1	1.0
rhinitis	0	1.3
<u>Gastrointestinal disorders:</u>		
abdominal pain	11.0	4.5
nausea	2.2	0.3
<u>Musculoskeletal and connective tissue disorders:</u>		
back pain	3.5	1.8
musculoskeletal pain	0.3	1.0
<u>Psychiatric disorders:</u>		
depression	2.1	1.0
<u>Nervous system disorders:</u>		
headache	5.8	6.5
<u>Reproductive system and breast disorders:</u>		
menstrual disorder	29.4	5.2
breast pain	3.2	1.6
genital discharge	1.3	0.7
ovarian cyst	0.6	1.3
vaginal infection	0.4	1.3
fibroadenoma of breast	0.2	1.1
<u>Skin and subcutaneous tissue disorders:</u>		
acne	2.8	0.9

Less Common Clinical Trial Adverse Drug Reactions

Additional adverse events reported in clinical trials with MIRENA occurring at a rate of less than 1.0% after either 3 or 60 months of use were:

Cardiac disorders:	hypertension, arrhythmia
Endocrine disorders:	lactation nonpuerperal, amenorrhoea
Gastrointestinal disorders:	diarrhea, toothache, tooth disorder, haemorrhoids, abdomen enlarged
General disorders and administration site conditions:	fatigue, edema, leg pain, influenza-like symptoms, pain
Immune system disorders:	allergic reaction, allergy
Injury, poisoning and procedural complications:	IUD complication
Infections and infestations:	otitis media (externa), pneumonia, pharyngitis, infection, fever, mastitis, cystitis
Metabolism and nutritional disorders:	weight increase
Musculoskeletal and connective tissue disorders:	tendonitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps):	breast neoplasm (benign), vaginal neoplasm (benign)
Nervous system disorders:	dizziness, vertigo, sciatica, migraine
Psychiatric disorders:	nervousness, emotional lability
Renal and urinary disorders:	dysuria, urinary incontinence, changes in micturition frequency
Reproductive system and breast disorders:	pre-menstrual tension, intermenstrual bleeding, ovarian disorder, endometritis, endometriosis, cervicitis, libido decreased, vulva disorder, uterine disorder (unspecified), dyspareunia, dysmenorrhoea, uterine fibroid, genital pruritis
Respiratory, thoracic and mediastinal disorders:	asthma
Skin and subcutaneous tissue disorders:	sweating increased, hypertrichosis, alopecia, eczema, seborrhoea, dry skin, skin disorder, pruritis
Surgical and medical procedures:	unspecified surgical/medical procedure

Post-Market Adverse Drug Reactions

Since market introduction in Canada in February 2001, 30 reports of suspected uterine perforation with MIRENA have been reported in over 111,000 units of MIRENA sold, for a reporting rate of 0.27/1000.

Undesirable effects are more common during the first months after insertion and subside during prolonged use. In addition to the adverse events observed in clinical trials, the following undesirable effects have been reported in users of MIRENA, although a causal relationship with MIRENA could not always be confirmed.

Infections:	genital infections
Gastrointestinal disorders:	pelvic pain, abdominal bloating
General disorders and administration site conditions:	expulsion
Reproductive system and breast disorders:	vaginal discharge, breast tension, mastalgia, uterine perforation
Skin and subcutaneous disorders:	hirsutism, rash, urticaria

DRUG INTERACTIONS

Drug-Drug Interactions

The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes, including primidone, barbiturates, phenytoin, carbamazepine, rifampicin and griseofulvin. The influence of these drugs on the efficacy of MIRENA (levonorgestrel-releasing intrauterine system) has not been studied, but it is not believed to be of major importance due to the local action of MIRENA.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose

Following insertion into the uterine cavity, MIRENA (levonorgestrel-releasing intrauterine system) is effective for up to five years. The in vivo dissolution rate is approximately 20 µg levonorgestrel per day initially, and diminishes over time to approximately 11 µg per day after five years. The mean dissolution rate is approximately 14 µg per day over five years.

If after 5 years, continued use of MIRENA is desired a new MIRENA system should be inserted immediately after the old one is removed.

Administration

Insertion, Removal and Replacement

Before insertion, the patient must be informed of the efficacy, risks and side effects of MIRENA. A physical examination including pelvic examination, examination of the breasts and cervical smear should be performed. Pregnancy and sexually transmitted diseases should be excluded and any genital infections must 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. The instructions for insertion should be followed carefully. The patient 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 should be inserted within seven days of the onset of menstruation. MIRENA may be replaced by a new system at any time during the cycle. The system can also be inserted immediately after first trimester abortion. Postpartum insertions should be postponed until six weeks after delivery. MIRENA is not suitable for use as a post-coital contraceptive.

Because irregular bleeding is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of MIRENA. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be undertaken.

MIRENA can be removed by gently pulling on 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.

The system should be removed after five years of use. If the patient wishes to continue using MIRENA, a new system can be inserted at the time of removal of the old one. If pregnancy is not desired, removal should be carried out during menstruation in women of fertile age provided that there appears to be a menstrual cycle. If the system is removed mid-cycle and the patient has had intercourse within a week, she is at risk of pregnancy unless a new system is inserted immediately following removal.

Insertion and removal may be associated with some pain and bleeding. The procedure may cause a fainting spell or precipitate a seizure in an epileptic patient.

Expulsion

Symptoms of the partial or complete expulsion of MIRENA may include bleeding or pain, however, a system may be expelled from the uterine cavity without the patient noticing it. Partial expulsion may decrease the effectiveness of MIRENA. Since MIRENA decreases menstrual flow, an increase in menstrual flow may indicate an expulsion. A displaced system should be removed. A new system can be inserted at that time and the patient should be advised on how to check for the presence of the system by feeling for the removal threads.

In a five-year clinical trial, the net cumulative expulsion rate ranged from 3.4 per 100 women in year one to 4.9 in year five. Expulsion rates for MIRENA are comparable to those observed for copper IUDs.

In the same clinical trial, the net cumulative removal rate due to pain ranged from 1.6 per 100 women in the first year to 4.2 in the fifth year.

Lost Removal Threads

If the removal threads are not visible upon follow-up examination, 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 be located by gently probing with a suitable instrument. If they cannot be found, the system may have been expelled or displaced (See **Expulsion**). Ultrasound or X-rays may be used to locate a displaced system (MIRENA is radiopaque).

Insertion Instructions

Because the insertion technique is different from intrauterine devices, it is important that physicians receive training on the correct insertion technique.

Physicians should become thoroughly familiar with the insertion instructions in their entirety before attempting insertion of MIRENA.

MIRENA is supplied sterile. It is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the pouch is damaged or open. Insert before the date indicated on the label.

MIRENA is to be inserted with the enclosed inserter into the uterine cavity within seven days of the onset of menstruation by carefully following these insertion instructions (Figure 1). It can be replaced by a new system at any time during the menstrual cycle.

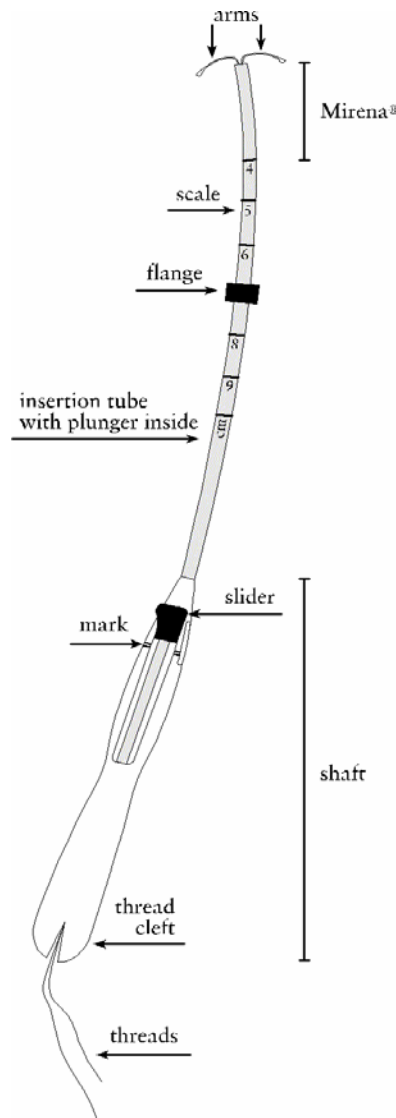


Figure 1

Conduct a gynecological examination of the patient to establish the size and position of the uterus and to exclude pregnancy or other genital tract contraindications for the use of MIRENA.

Preparation for Insertion

1. Visualize the cervix by means of a speculum and thoroughly cleanse the cervix and vagina with a suitable antiseptic solution. Grasp the upper lip of the cervix with a suitable holding forceps.
2. Gentle traction on the holding forceps has been shown to align the cervical canal with the uterine cavity. The forceps should remain in position throughout the insertion procedure to maintain gentle traction on the cervix against the pushing force of the insertion.
3. Gently move a uterine sound into the uterine cavity to the fundus to determine the direction of the cervical canal and the depth of the uterine cavity, and to exclude a uterine septum, synechiae and submucosal fibroids. Should the cervical canal be too narrow, consider the need for dilatation and the use of analgesics or paracervical block.

Insertion

1. Open the sterile package enough to reveal the shaft of the inserter. Wearing sterile gloves, make sure that the slider is in the furthestmost position. Grasp the shaft as illustrated in Figure 2 and check that the arms of the system are in a horizontal position (shape of a T). If they are not, align them on the sterile surface of the MIRENA packaging tray (Figure 2).

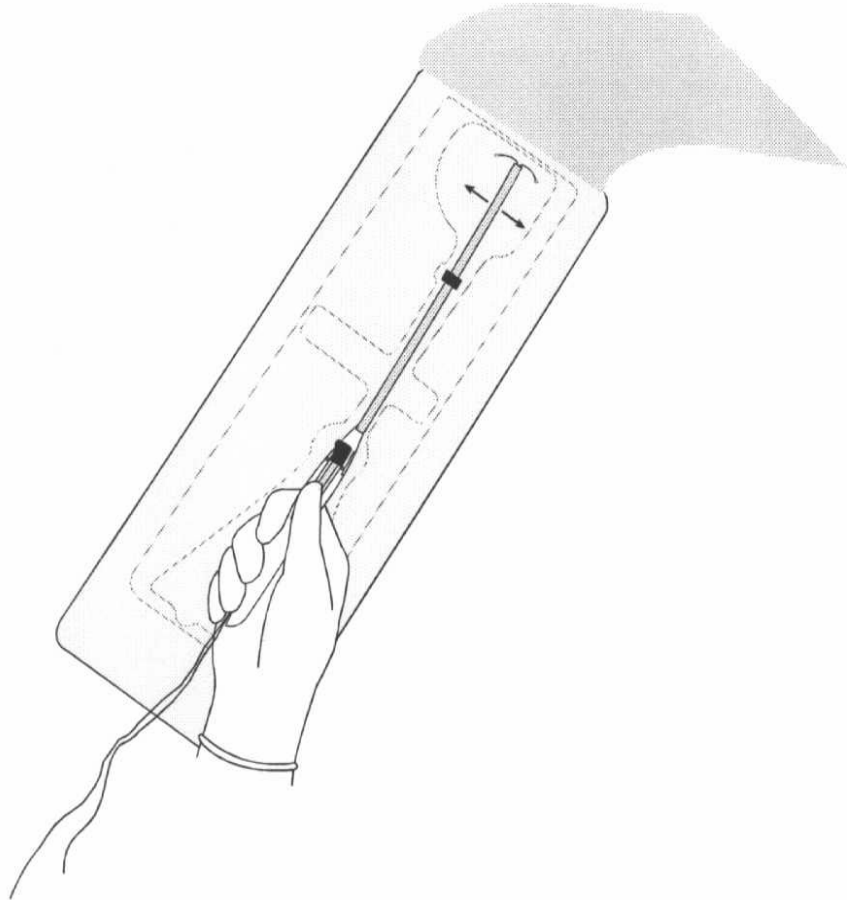


Figure 2

2. Pull on the threads to position the arms of the MIRENA system into the inserter tube (Figure 3). Note that the knobs at the end of the arms now close the open end of the inserter.

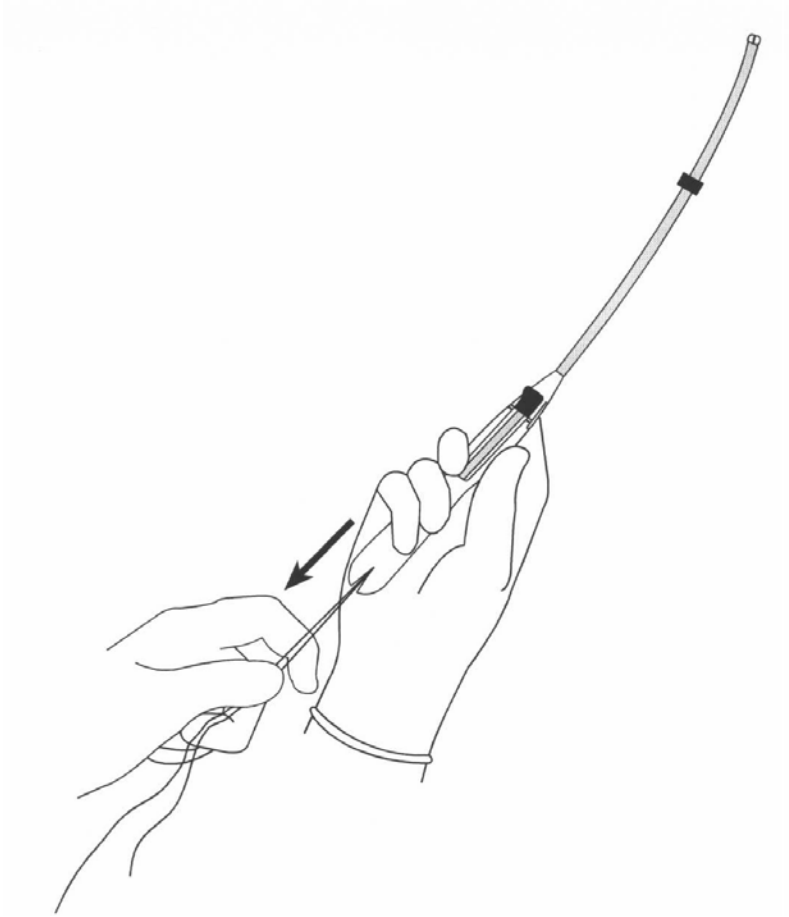


Figure 3

3. Fix the threads tightly in the cleft at the end of the inserter shaft (Figure 4).

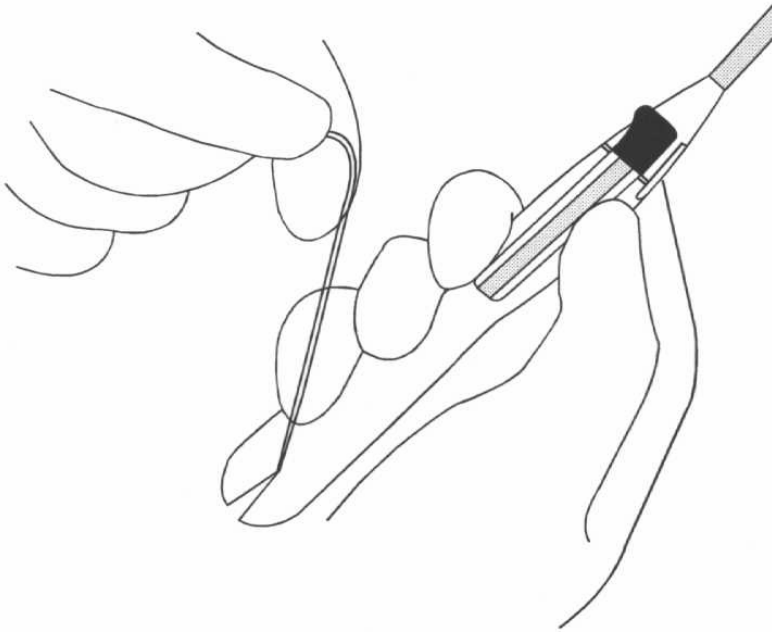


Figure 4

4. Ensure that the arms are in the correct position and that they will fold out horizontally. If not, open the arms by pulling the slider back to the raised mark on the shaft (Figure 5). Align the open arms on a sterile surface as shown in Figure 2. Return the slider to its previous position. Check that the threads are still tight and that the arms have moved back into the inserter.

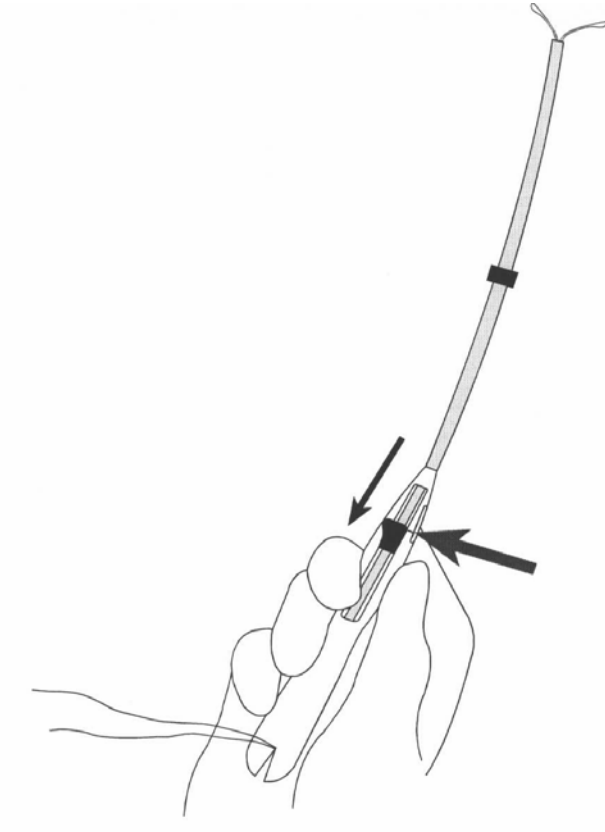


Figure 5

5. Set the flange at a distance from the knobs on MIRENA corresponding to the uterine sound measure by using the scale marked on the inserter tube (Figure 6). Note that this measurement is from the end of the inserter to the top edge of the flange.

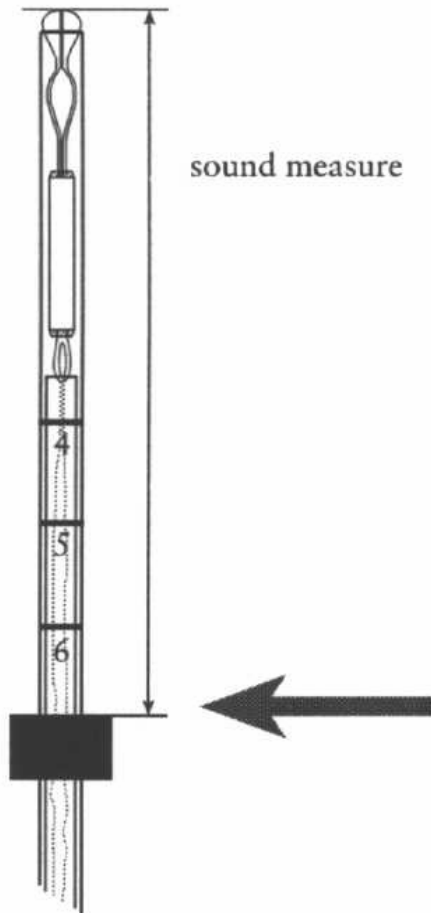


Figure 6

- MIRENA is now ready to be inserted. Hold the slider with the forefinger or thumb firmly in the most distal position. Move the inserter carefully through the cervical canal into the uterus until the flange is situated at a distance of about 1.5 – 2 cm from the cervix to give sufficient space for the arms to open (Figure 7). **Do not force the inserter.**

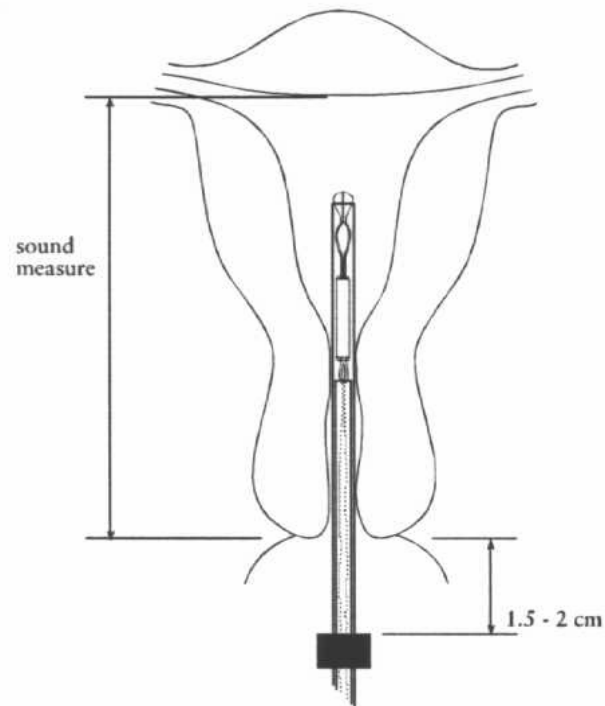


Figure 7

7. While holding the inserter steady, release the arms of MIRENA (Figure 8) by pulling the slider back until it reaches the raised mark on the shaft (Figure 5).

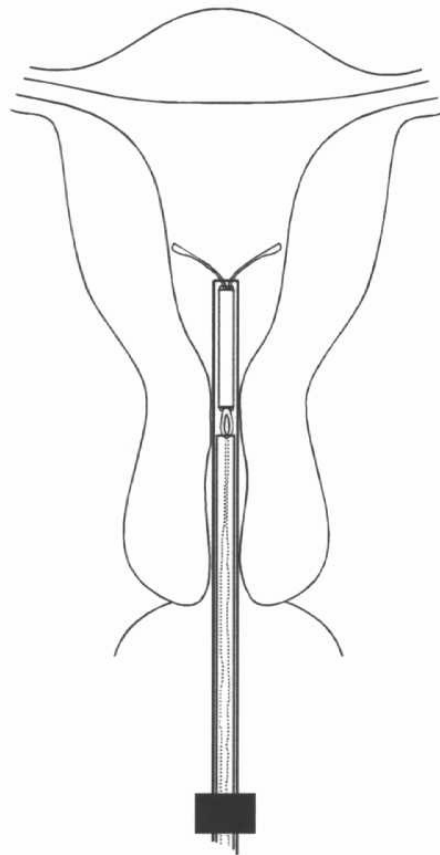


Figure 8

8. Holding the slider firmly, push the inserter gently inward until the flange touches the cervix. MIRENA should now be at the fundus (Figure 9).

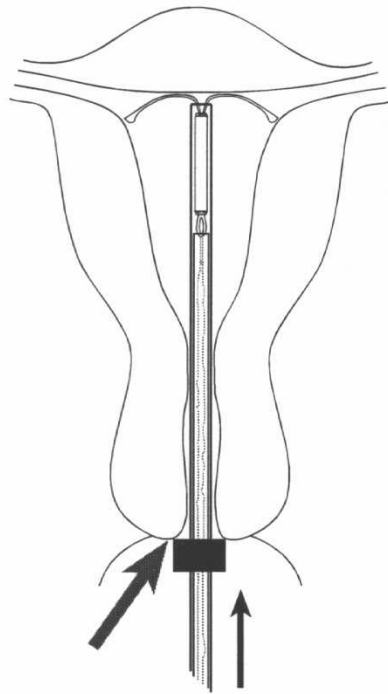


Figure 9

9. Holding the inserter firmly in position, release MIRENA by pulling the slider all the way back. The threads will uncoat automatically (Figure 10).

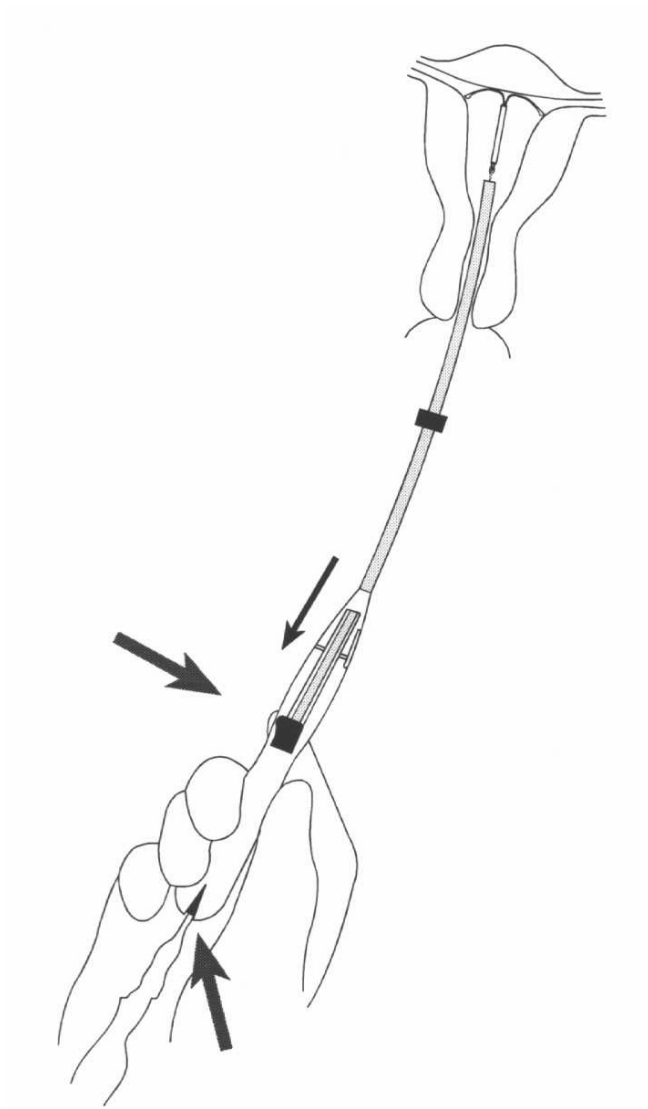


Figure 10

10. Remove the inserter from the uterus. Cut the threads to leave about 2 cm visible outside the cervix (Figure 11).

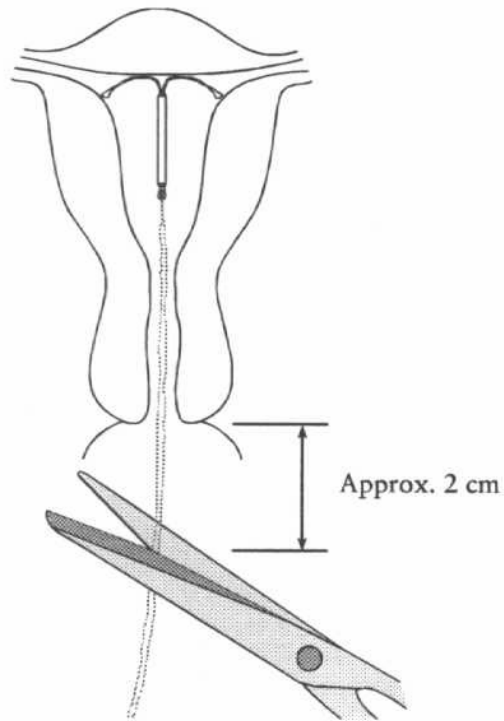


Figure 11

If there is any doubt that the system is not in the correct position, verify with ultrasound or X-ray. If necessary, remove the system and insert a new one. A removed system must never be re-inserted.

Use of sanitary pads

The use of sanitary pads is recommended. If tampons are used, they should be changed carefully to avoid inadvertently pulling the MIRENA removal threads.

Removal of MIRENA

MIRENA can be removed by pulling the threads with forceps.

A MIRENA system should not remain in the uterus longer than 5 years.

ACTION AND CLINICAL PHARMACOLOGY

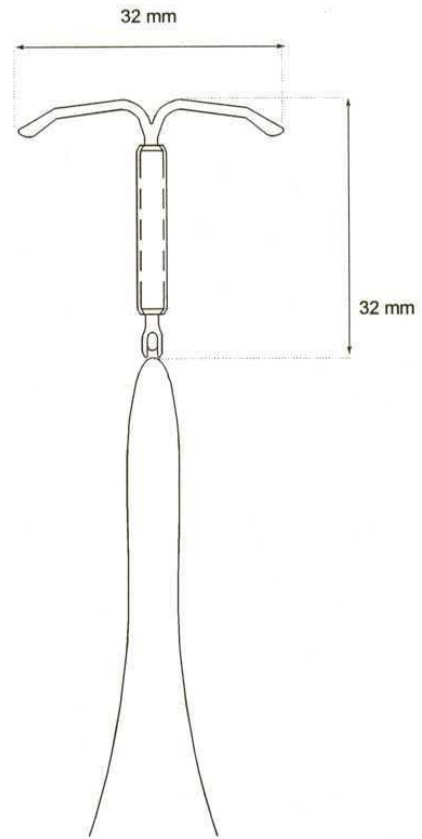
Mechanism of Action

MIRENA (levonorgestrel-releasing intrauterine system) consists of a small polyethylene T-shaped frame with a cylindrical reservoir containing levonorgestrel around the vertical arm of the T frame. After insertion into the uterus, MIRENA releases levonorgestrel continuously for up to five years. Intrauterine administration allows a very low daily dosage, as the hormone is released directly to the target organ. MIRENA contains a total of 52 mg levonorgestrel and has an initial intrauterine release rate of 20 µg per day that diminishes over time to approximately 11 µg per day after 5 years.

polyethylene T-shaped frame

cylindrical reservoir containing levonorgestrel

polyethylene removal threads



MIRENA
(levonorgestrel-releasing intrauterine system)

Pharmacodynamics

The contraceptive action of MIRENA is due mainly to the local progestogenic effect of levonorgestrel on the uterine cavity. It produces a strong antiproliferative effect on the endometrium and causes a thickening of the cervical mucus which prevents passage of sperm through the cervical canal. Ovulation is inhibited in some women. Clinical trials with MIRENA were performed in parous women mainly over the age of 18 years; results from these studies involving more than 7,600 woman-years of use indicate an overall Pearl index of 0.11. The 5-year cumulative gross pregnancy rates in these trials ranged from 0 to 1.2 per 100 women.

Normal menstruation returns quickly after removal of MIRENA. After five years of use in clinical trials, the return of normal cyclical endometrial morphology was observed to occur from one to three months after removal of MIRENA. The use of MIRENA does not alter the course of future fertility; nearly 90% of women wishing to become pregnant conceive within 24 months after removal of the system.

The duration and volume of menstrual bleeding and menstrual blood loss gradually decreases during the first few months of use. With continued use, bleeding patterns vary from regular scanty menstruation in some women to oligomenorrhea or amenorrhea in others.

The menstrual bleeding patterns of 1,495 women enrolled in a clinical trial were examined for the first 12 months after MIRENA insertion. The number of combined days of vaginal bleeding or spotting decreased from a mean of 16.1 days during the first month, to a mean of 3.8 days during the 12th month (see Table 2).

Table 2: Number of Combined Vaginal Bleeding / Spotting Days During the first 12 Months After MIRENA Insertion

Interval (in 30-day segments)												
Days												
	1 - 30	31 - 60	61 - 90	91 - 120	121 - 150	151 - 180	181 - 210	211 - 240	241 - 270	271 - 300	301 - 330	331 - 360
N	1,495	1,472	1,422	1,297	1,237	1,199	1,168	1,142	1,113	1,079	1,055	988
mean	16.1	11.2	8.5	7.1	6.4	5.8	5.2	4.8	4.5	4.3	4.1	3.8

The altered menstrual bleeding pattern that occurs with MIRENA use is a result of the direct action of levonorgestrel on the endometrium and is not due to the suppression of the ovulatory cycle. There is no clear difference in follicle development, ovulation, or estradiol and progesterone production in women with different bleeding patterns. Ovarian function is normal and estradiol levels are maintained even when users of MIRENA are amenorrheic.

The effect of MIRENA on ovarian function depends on plasma levonorgestrel levels achieved. While marked interindividual variation is observed, plasma concentrations are relatively constant within each individual. Patterns of ovarian function in women using MIRENA include normal ovulatory cycles, anovulatory cycles with some inhibition of estradiol production, anovulation with high follicular activity and ovulation with an inadequate luteal phase. In general, anovulatory cycles correlate with higher plasma levels of levonorgestrel, and are more frequent in the first year of MIRENA use. Functional ovarian cysts may occur in relation to pre-ovulatory arrest of follicular development in any woman, and are associated with progestogen-only methods of contraception.

Endometrial histology has been investigated in clinical studies examining the intrauterine release of levonorgestrel at rates ranging from 10 to 40 µg/day. Subjects with anywhere from 3 to 84 months of exposure to continuous levonorgestrel release showed endometrial glandular atrophy and decidualized stroma throughout the period. Local inflammation and focal necrosis compatible with the intrauterine mode of administration were observed.

In one study, cervical histology was evaluated by examining cervical smears from 1,355 women using MIRENA over a period of five years. A total of twelve smears indicated moderate to severe cervical dysplasia. Large multi-centre studies have not detected differences in cervical cytology between women using MIRENA and those using copper IUDs.

Pharmacokinetics

Absorption

The intrauterine release of levonorgestrel results in the absorption of the drug into the systemic circulation.

Distribution

The drug can be detected in plasma within 15 minutes of insertion and maximum concentrations are seen within a few hours. Following intrauterine insertion of MIRENA, the initial release rate of levonorgestrel is 20 µg per day. This provides stable plasma levonorgestrel concentrations which, after the first few weeks, stabilize at between 150 to 200 pg/mL in women of fertile age. After 12, 24 and 60 months of use in young women, plasma levonorgestrel concentrations of 180 ± 66 pg/mL, 192 ± 140 pg/mL, and 159 ± 60 pg/mL were observed, respectively. Because of the low drug levels in plasma, the systemic effects of the progestogen are minimized.

Orally administered levonorgestrel is rapidly and completely absorbed and the absolute bioavailability is about 90%. Levonorgestrel is bound to serum albumin and to sex hormone-binding globulin (SHBG). The relative distribution (free, albumin-bound, SHBG-bound) depends on the SHBG concentration in the serum. Only about 2.5% of the total serum drug levels are

present as free steroid, but 47.5% and 50% are bound to SHBG and albumin respectively. For levonorgestrel, a mean volume of distribution of approximately 137 litres and a metabolic clearance rate from serum of about 5.7 L/hr were reported.

Metabolism and Excretion

The terminal half-life in serum is in the range of 14-20 hours after single-dose administration. Levonorgestrel is excreted as metabolites at about equal proportion in urine and feces. The metabolites have little or no pharmacological activity. The principal metabolite in urine is tetrahydronorgestrel which accounts for approximately 25% of the radioactivity recovered from the urine after administration of radiolabeled levonorgestrel. About 0.1% of the dose is excreted in breast milk.

STORAGE AND STABILITY

Store at room temperature (between 15°C and 30°C). Protect from moisture and direct sunlight.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each MIRENA (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel USP in a cylindrical-shaped reservoir composed of a matrix of levonorgestrel and polydimethylsiloxane. The reservoir is mounted on the vertical arm of a T-shaped frame made of polyethylene and covered with a rate-controlling membrane of polydimethylsiloxane and silica. The T-frame is pigmented with barium sulphate. The polyethylene removal threads attached to the T-frame are pigmented with black iron oxide.

MIRENA is available in a carton of one sterile unit. Each MIRENA is packaged in a pouch within an inserter.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

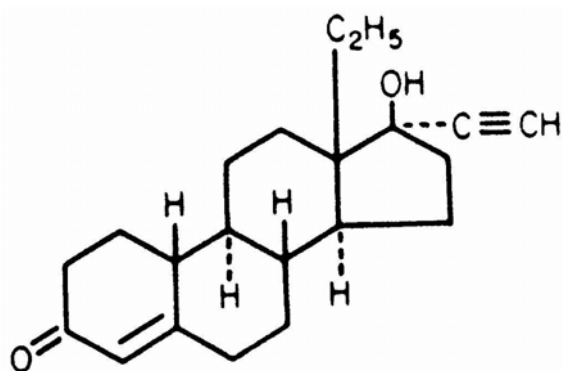
Proper name: levonorgestrel

Chemical name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17 α)(-)

Molecular formula: C₂₁ H₂₈ O₂

Molecular Mass: 312.45

Structural formula:



Physicochemical properties: Levonorgestrel is a white to off-white crystalline powder, practically insoluble in water and slightly soluble in ethanol, in vegetable oils, in chloroform, in ether and in alkaline solutions. The melting range is between 232°C and 239°C.

CLINICAL TRIALS

Contraceptive Efficacy

Clinical studies with MIRENA consistently show high contraceptive efficacy. The contraceptive efficacy of MIRENA was studied in three clinical trials in which a total of 2,379 women were enrolled. One trial compared MIRENA (n=1,821) to a copper IUD (n=937) over a period of 5 years with a resultant Pearl index of 0.09 for MIRENA and 1.26 for the copper IUD. After completion of this trial, 168 women from the MIRENA group enrolled in a second clinical trial and had a new MIRENA system inserted for four years. Results after 6,404 woman-months of experience revealed a Pearl index of 0. A third MIRENA trial was non-comparative, and enrolled 390 women for 5 years with a resultant Pearl index of 0.24. Combined data from three clinical trials provides 91,133 woman-months of experience. There were a total of 8 pregnancies, giving a Pearl rate of 0.11.

Continuation Rate

The continuation rate for MIRENA in a five-year clinical trial in 390 women, was 56%. The desire to become pregnant was the most common reason for discontinuing MIRENA (about 20% of all discontinuations). Other discontinuations were due to medical reasons (predominantly hormonal, menstrual problems and pain).

DETAILED PHARMACOLOGY

Pharmacodynamics

Levonorgestrel is a 19-nortestosterone derivative with potent progestogenic effects, but no significant estrogenic activity.

In rabbits, evidence of transformation of the endometrium was observed after subcutaneous administration of 0.01 mg levonorgestrel corresponding to 2 µg/kg/day. Transformative effects are also histologically recognizable in the rabbit endometrium when levonorgestrel is administered orally in doses ranging from 0.03 to 0.3 mg per animal corresponding to approximately 6 to 60 µg/kg/day.

In pregnant rats, ovariectomized within the first 4 days after conception, the subcutaneous administration of 0.002 mg levonorgestrel had a blastocyst-maintaining effect. The anti-estrogenic or progestogenic activity of levonorgestrel has also been demonstrated in various test models in rats and mice, the potency of levonorgestrel is significantly higher than progesterone and about 83 times stronger than chlormadinone acetate.

Levonorgestrel does not have any significant estrogenic activity and androgenic effects are only detectable after large doses. Levonorgestrel also influences the gonadotrophic function of the anterior lobe of the pituitary gland in all experimental tests.

Like other progestogens, relative large doses of levonorgestrel lead to increases in insulin secretion in rats and dogs.

TOXICOLOGY

Toxicology studies were performed on all the components of MIRENA: the "unfilled polymer", the "levonorgestrel-releasing reservoir", the "membrane tubing", the polyethylene "T-body" and the polyethylene "removal threads".

The unfilled polymer is the polydimethylsiloxane (PDMS) polymer after peroxide catalysis. The unfilled polymer is mixed in an equal ratio with levonorgestrel, to form the levonorgestrel-releasing reservoir. The unfilled polymer is also mixed with inert colloidal silica to form the membrane tubing, which covers the levonorgestrel reservoir and serves to control the release rate of levonorgestrel from MIRENA.

Acute Toxicology

The USP systemic injection test in mice on the unfilled polymer, membrane tubing, T-body and removal threads did not show any signs of toxicity.

Mutagenicity

Extracts of the unfilled polymer, membrane tubing, T-body and removal threads were evaluated for mutagenic potential in the following in vitro and in vivo tests: reverse gene mutation in vitro in four *Salmonella typhimurium* and one *Escherichia coli* strains of bacteria, TK mutation test in mouse lymphoma L5178Y cells in vitro, chromosomal aberrations in human peripheral blood lymphocytes in vitro, and the induction of micronuclei in the bone marrow of mice.

Extracts of the unfilled polymer did not show any evidence of mutagenic or clastogenic activity in vitro and did not induce chromosomal changes or other damage to micronucleus formation in polychromatic erythrocytes in vivo after intraperitoneal administration to mice.

Saline and aqueous extracts of the levonorgestrel-releasing reservoir were negative except for the chromosomal aberration test in CHO cells. Treatment of cultures of CHO cells with the highest dose of DMSO extracts of the levonorgestrel-releasing reservoir, which were also precipitating, resulted in small increases in the number of cells with aberrations (attributed to polyploidy) in a single culture at the 20 and 44 hour sampling times during the second of two independent experiments. Pure levonorgestrel was not mutagenic or clastogenic in any of the tests. No clastogenic effect was detected for saline or arachis oil extracts tested in vivo in the mouse micronucleus test. The results of these studies indicate that it is very unlikely that the materials used in the levonorgestrel-releasing reservoir of MIRENA would cause genetic damage in humans under the conditions of clinical use.

Saline and non-aqueous extracts of the T-body containing low-density polyethylene (with 20-24% barium sulphate), and of removal threads containing high-density polyethylene (with 1% iron oxide) were not mutagenic or clastogenic in vitro and did not induce chromosomal changes or

other damage to micronucleus formation in polychromatic erythrocytes in vivo after intraperitoneal administration to mice.

Local Tolerance Studies

Saline and non-aqueous extracts of the unfilled polymer, membrane tubing, T-body and removal threads were evaluated for biocompatibility using the following in vitro and in vivo test systems: cytotoxicity test in mouse fibroblasts, guinea pig maximization test, intracutaneous test in rabbits, systemic injection test in mice, pyrogen testing, muscle implantation test in rabbits and a test for hemolysis.

The results of these tests indicated acceptable biocompatibility of both the unfilled polymer and the membrane tubing. No remarkable in vitro cytotoxicity or hemolysis was detected. There was no evidence of delayed contact hypersensitivity, intracutaneous injection site irritation or test article-related clinical signs of systemic toxicity including pyrogenicity, after treatment with saline or sesame oil extracts.

In the muscle implantation test for the unfilled polymer, very thin encapsulation was observed on the test article implants and in one of the negative control implants. This was correlated with minimal microscopic changes (few to moderate inflammatory cells) in both test and control implants, indicating that the unfilled polymer was well tolerated.

A similar result was observed in the muscle implantation test for the membrane tubing, a very thin encapsulation of the test and control implants which was detected at necropsy on Day 90 was correlated with minor microscopic changes (fibrosis), indicating that the membrane tubing was well tolerated.

With regard to the low-density polyethylene T-body, no remarkable in vitro cytotoxicity or hemolysis was detected. There was no evidence of delayed contact hypersensitivity, intracutaneous injection site irritation or test article-related clinical signs of systemic toxicity, including pyrogenicity after treatment with saline or sesame oil extracts. In the muscle implantation test for the T-body, a very thin encapsulation of one test article implant which was detected at necropsy on Day 90 was correlated with only minor microscopic changes (minimal to slight fibrosis, minimal necrosis and minimal hemorrhage). The same test for the removal threads showed a very thin encapsulation of the test article and USP negative control plastic implants which were detected at necropsy on Day 90, and were correlated with only minor histology (minimal to slight fibrosis). The results of these tests indicate that both the T-body and the removal thread were well tolerated.

Long-term Toxicity

A one-year intrauterine toxicity study of MIRENA was conducted in Rhesus monkeys using a smaller modified version of the system delivering 12.3 µg levonorgestrel per day. The raw materials were the same as those used in the formulation of MIRENA with the exception that the polydimethylsiloxane polymer was catalyzed using stannous octoate rather than peroxide. The

system caused suppression of ovulation in four of eight monkeys, reduced uterine weights and resulted in the expected decidual endometrial changes. Cervical morphology was within normal limits and there was a slight shortening of partial thromboplastin time (which was also seen in the monkeys implanted with inert devices). Plasma levels of levonorgestrel varied between 0.1 and 0.4 ng/mL.

Overall, there was no significant difference observed between the monkeys with the levonorgestrel-releasing intrauterine system and those with the inert intrauterine system used in the study.

Reproduction and Teratology

A smaller modified version of MIRENA was used for a reproductive toxicology study in rabbits. It consisted of a cylinder (diameter 2.4 mm, length 7 mm) with an inner core (5 mm) containing 12 mg levonorgestrel mixed with polydimethylsiloxane polymer, with a polydimethylsiloxane polymer membrane fitted over the core for release rate control. The release rate was calculated to be 3.5 µg levonorgestrel per day. One system was put into each uterine horn of the pregnant rabbits.

Treatment did not have any adverse effect on litter parameters such as body weight and gross pathology, embryonic or fetal development. One rabbit in the treatment group had a hemorrhagic endometrium observed at Caesarean section. No treatment-related adverse effects were observed.

REFERENCES

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2. Nilsson, C.G. and Lahteenmaki, P. Recovery of Ovarian Function After the Use of a d-Norgestrel-releasing IUD. *Contraception* 1977; 15:389-400.
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PART III: CONSUMER INFORMATION

**MIRENA
Levonorgestrel-releasing Intrauterine System**

This leaflet is part III of a three-part "Product Monograph" published when MIRENA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MIRENA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- to prevent pregnancy

For preventing pregnancy, MIRENA is as effective as oral contraceptives. Clinical trials found that there were about 2 pregnancies per year for every 1,000 women using MIRENA.

What it does:

MIRENA is an intrauterine system which prevents pregnancy by slowly releasing small amounts of a synthetic sex hormone known as levonorgestrel into the uterus. Levonorgestrel is a hormone commonly used in combination oral contraceptives (the "Pill") and is similar to progesterone, a sex hormone produced naturally by the body.

MIRENA works by slowly releasing levonorgestrel into the uterus at a rate of approximately 20 micrograms per day. This small amount of levonorgestrel prevents pregnancy by:

- reducing the normal monthly thickening of the lining of the uterus.
- thickening the cervical mucus which prevents passage of sperm through the cervical canal (opening to the uterus).

MIRENA contains a total of 52 mg of levonorgestrel which is enough hormone to prevent pregnancy for five years.

When it should not be used:

- if you are pregnant, or if you suspect that you may be pregnant.
- if you have or have had pelvic inflammatory disease (see the paragraph in this leaflet titled "Infections")
- if you have an infection of your lower genital tract
- if you have had a womb infection after delivering a baby
- if you have bleeding from the vagina that has not been explained
- if you have a condition of the uterus that distorts the uterine cavity, such as large fibroids
- if you have an infection of the cervix (neck of the womb)
- if you have cell abnormalities in the cervix (your doctor can tell you if you have this)
- if you have liver problems, including liver cancer

- have had a womb infection after having an abortion during the past 3 months
- have any allergies to the hormone levonorgestrel, or to any of the other ingredients of MIRENA, or to components of the container (see the section in this leaflet titled "What the important nonmedicinal ingredients are")
- if you have bacterial endocarditis (a doctor will have told you if you have this)
- if you have immunodeficiency (a doctor will have told you if you have this)
- if you have cancer affecting the blood, or if you have leukemia
- if you have or have had trophoblastic disease (a doctor will have told you if you have this).

What the medicinal ingredient is:

levonorgestrel

What the important nonmedicinal ingredients are:

barium sulphate, iron oxide, polydimethylsiloxane, polyethylene, silica.

What dosage form it comes in:

Each MIRENA (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel to deliver up to 20µg levonorgestrel per day, and is packaged in a pouch within an insertion device.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

MIRENA DOES NOT PROTECT against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms.

BEFORE you use MIRENA, talk to your doctor or pharmacist if you:

- are breast-feeding
- have ever had an ectopic pregnancy (development of a fertilized egg outside the uterus) (see the paragraph in this leaflet titled "Ectopic pregnancy")
- have had surgery on your fallopian tubes.
- have a history of ovarian cysts (see the paragraph in this leaflet titled "Cysts on the ovary")
- have an unusual menstrual bleeding pattern.
- have an unusual or unpleasant (e.g. smelly) vaginal discharge or vaginal itching.
- have had a stroke, heart attack or any heart problems.
- have or have had jaundice (a yellowing of the whites of the eyes and/or nails)
- are diabetic or have a family history of diabetes (see the following paragraph in this leaflet titled "Diabetes"), have

high blood pressure or abnormal blood lipid levels.

- have a history of blood clots (thrombosis).
- are on long-term steroid therapy or are taking any other medications.
- have a history of migraine, dizziness or blurred vision.
- have severe headaches.
- have a history of depression
- wear contact lenses
- have an abnormality of your heart or if you have any problem with your heart valves

MIRENA is not the method of first choice for young women who have never been pregnant, nor for postmenopausal women with shrinking of the womb.

Diabetes

In diabetic users of MIRENA, the blood glucose concentration should be monitored.

Infections

A serious pelvic infection called pelvic inflammatory disease (PID) may occur in some users of MIRENA. PID is usually sexually transmitted. You have a higher chance of getting PID if you or your partner have sex with other partners. PID can cause serious problems such as infertility, ectopic pregnancy, or constant pelvic pain. PID is usually treated with antibiotics, however, more serious cases of PID may require surgery. Tell your doctor right away if you have any of these signs of PID: long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal (stomach area) pain, painful sex, chills or fever.

Ectopic pregnancy

Ectopic pregnancy (development of a fertilized egg outside the uterus) is possible, as it is in women using no contraception, but is highly unlikely. You should tell your doctor if you have lower abdominal (tummy) pain especially if you have missed a period or have unexpected bleeding. This might be a sign of ectopic pregnancy.

Cysts on the ovary

Cysts on the ovary commonly occur in women using MIRENA. These cysts usually disappear on their own within a few months. However, cysts can sometimes cause pain and may need medical attention.

Driving or Using Machines

The effects of MIRENA on the ability to drive or to use machines have not been studied.

Uterine Perforations

In rare cases (occurring at a rate of between 1/1,000 and 1/10,000), and most often during insertion, MIRENA may penetrate or perforate the wall of the uterus. If this happens, the system must be removed.

Abnormal Blood Clotting

Some studies have suggested that women who use progestogen-only oral contraceptives might have a slightly higher risk of blood clots, however the results are not certain. You should discuss risk factors for blood clots with your doctor since blood clots can be life threatening or cause serious disability.

Can I breast-feed while using MIRENA?

Small quantities of levonorgestrel, the medicinal ingredient in MIRENA, have been found in the milk of breast-feeding women using MIRENA; however, there does not appear to be a detrimental effect on growth or development of breast-fed infants whose mothers started using the product six weeks after delivery.

How will MIRENA affect my periods?

MIRENA will affect your menstrual cycle. You might experience frequent spotting (a small amount of blood loss) or light bleeding in addition to your periods for the first 3 to 6 months. In some cases, you may have heavy or prolonged bleeding during this time.

Overall, you are likely to have a gradual reduction in the number of bleeding days and in the amount of blood loss each month. Some women using MIRENA eventually find that their periods stop altogether.

When the system is removed, periods return to normal.

What if I stop having periods?

Gradually, over time, your menstrual period may disappear. This is because of the effect of the hormone on the lining of the uterus. The normal monthly thickening of the uterine lining with blood does not happen, therefore there is little or no bleeding, as happens during a usual menstrual period. It does not necessarily mean you have reached menopause or are pregnant. Your own hormone levels remain normal.

If, however, you are having regular menstrual periods and then do not have one for 6 weeks or longer, it is possible that you may be pregnant. You should speak to your doctor.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription.

Hormonal contraceptives may become less reliable if you are also taking drugs that affect the liver (such as primidone, barbiturates, phenytoin, carbamazepine, rifampicin and griseofulvin) at the same time. The influence of these drugs on the reliability of MIRENA has not been studied, but is unlikely since MIRENA releases a very small amount of hormone, and delivers inside the uterus.

The T-frame of MIRENA contains barium sulphate, which makes it visible in X-ray examinations.

PROPER USE OF THIS MEDICATION

Usual Dose

What it looks like:



MIRENA consists of a small white T-shaped frame made from soft, flexible plastic. The vertical and horizontal arms of the T are approximately 3 cm in length. The vertical arm is surrounded by a narrow cylindrical shaped reservoir that contains levonorgestrel. Two fine plastic threads are attached to the tip of the vertical arm. These threads are intended to be used for removal of the system and also serve to check its presence once it is in place.

How is MIRENA inserted?

Before MIRENA is inserted, your doctor should perform an examination, which may include a Pap smear, a breast examination and other tests, e.g., a test to make sure you aren't pregnant, and tests for infections, including sexually transmitted diseases, as necessary. Infections must be successfully treated before MIRENA is inserted.

You will also have a pelvic examination to determine the position and size of your uterus. Following this, your doctor will insert the thin flexible plastic tube of the insertion device containing MIRENA into your uterus. At this point you may feel a little discomfort.

Once MIRENA is in the correct position, your doctor will withdraw the tube leaving the system in place in the uterus. Finally, your doctor will trim the removal threads to a suitable length.

After insertion you may feel some cramp-like menstrual pain; however, this usually disappears within a few days.

Most women find that the insertion procedure causes minor discomfort, however, for some it may be more uncomfortable. If concerned, you may wish to discuss the need for a painkiller or local anesthetic with your doctor. Some women may feel faint after the system is inserted, but this feeling subsides after a short rest. The insertion procedure may precipitate a seizure in epileptic patients.

It is uncommon but, part or all of the system may penetrate the wall of the uterus during insertion and come to rest outside the uterus. If this happens the system must be removed.

When should MIRENA be inserted?

The system should be inserted during your period or within seven days of it starting. When replacing an existing system for a new one, it is not necessary to wait for your period.

Following childbirth, MIRENA should not be fitted until 6 weeks after delivery.

How long does insertion take?

The insertion procedure usually takes a few minutes after your doctor has completed the pelvic examination.

How quickly does MIRENA start to work?

You will be protected from pregnancy as soon as insertion of the system is complete, however, it is best to wait 24 to 48 hours before having sexual intercourse.

How often should I have MIRENA checked?

You should have the system checked approximately 6 weeks after it is fitted, again at 12 months and then once-a-year until it is removed. MIRENA can stay in place for 5 years before it must be removed.

You should see your doctor if:

- you cannot feel the threads anymore.
- you can feel the lower end of the system.
- you think you are pregnant.
- you have persistent abdominal pain, fever or unusual discharge from the vagina.
- you or your partner feels pain or discomfort during sexual intercourse.
- there are sudden changes in your menstrual periods, for example, if your menstrual periods stop completely and then you have persistent bleeding or pain, or if you have little or no menstrual bleeding and then you start bleeding heavily.
- you have other medical problems, such as migraine headaches or intense headaches that recur, sudden problems with vision, jaundice (a yellowing of the whites of the eyes or skin) or any of the other symptoms listed in the table titled Serious Side Effects in this leaflet, or if you are told you have high blood pressure.

- you are diagnosed with any of the medical conditions listed in the “Who should not use this medication” and “Warnings and precautions” sections of this leaflet.

How can I check if MIRENA is in place?

After each menstrual period or about once a month, you should check by feeling if the two threads are still in place. Your doctor will show you how to do this. Do not pull on the threads as you may accidentally pull the system out.

If you cannot feel the threads, see your doctor and in the meantime use another method of contraception. You should also see your doctor if you can feel the lower end of the system itself.

Can I become pregnant while using MIRENA?

Although it is very rare, it is possible for you to become pregnant with MIRENA in place.

If you do not have your period at the normal time and have other symptoms of pregnancy (e.g. nausea, tiredness, breast tenderness), you should see your doctor for an examination and pregnancy test.

If you become pregnant with MIRENA in place, you should have it removed as soon as possible. If it is left in place during pregnancy, the chances of having a miscarriage or premature delivery increases. The effect of levonorgestrel on a developing infant is not well known, therefore a detrimental effect cannot be completely ruled out. You may wish to consider termination of the pregnancy. Your doctor will advise you.

What if I want a baby?

If you want a baby, ask your doctor to remove MIRENA. Your usual level of fertility will return very quickly after the system is removed. Nearly 90% of women wishing to become pregnant conceive within 24 months after removal of the system.

Will MIRENA interfere with sexual intercourse?

During sexual intercourse, you or your partner should not be able to feel MIRENA. If you can feel MIRENA, or any pain or discomfort that you suspect may be caused by it, then you should not have sexual intercourse until you see your doctor to verify it is still in the correct position.

Can tampons be used?

Use of sanitary pads is recommended. If tampons are used, you should change them with care so as not to pull the threads of MIRENA.

Can MIRENA fall out?

It is unlikely, but possible that MIRENA can come out either completely or partially. If this happens you are not protected against pregnancy.

An unusual increase in the amount of bleeding during your period might be a sign that this has happened. You can check that MIRENA is in place by feeling for the threads as explained by your doctor.

If you think it has come out, use another method of contraception until you see your doctor.

Removal of MIRENA

You should see your doctor when you want to have MIRENA taken out. You can do this at any time and removal is very easy, however, you should be aware that you may become pregnant upon removal of the system if you have had sexual intercourse during the previous week.

Tell your doctor if you have had sexual intercourse during the preceding week.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Cysts on the ovary and menstrual bleeding irregularity (or of increased amount), are the most common side effects of MIRENA during the first months after the system is inserted, but these effects should decrease over time. Other side effects might include lower abdominal pain, headache, acne or other skin problems, tender breasts, backache, depression, a feeling of sickness, or menstrual pain.

The following side effects generally do not require medical attention, and will usually go away as your body adjusts to MIRENA:

Common: changes in bleeding (frequent, prolonged or heavy bleeding, spotting) nausea (feeling sick), acne, breast pain or swelling, weight gain.

Uncommon: Hair loss or excessive body hair, decreased sexual desire.

If you think you are reacting poorly to MIRENA or are having other problems, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM			
Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Vaginal bleeding	✓	
	Symptoms of vaginal infection, such as itching, or unusual or increased vaginal discharge		✓
	Headache	✓	
	Dizziness		✓
	Abdominal pain		✓
	Pelvic or back pain		✓
	Feeling depressed or nervous		✓
	Skin rash, hives, eczema (itchy skin lesions)		✓
Expulsion of MIRENA		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM			
Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Uncommon	Severe lower abdominal pain which may be together with bleeding, possibly meaning perforation of the uterus.		✓
	Migraine		✓
	Feeling of fullness or tightness in the abdomen	✓	
	Itching of the skin	✓	
	Persistent lower abdominal pain, together with fever or unusual discharge from the vagina, possibly meaning pelvic infection.		✓
	Persistent lower abdominal pain, together with nausea or breast tenderness and/or vaginal bleeding, possibly meaning intrauterine pregnancy, miscarriage, or extrauterine pregnancy.		✓

This is not a complete list of side effects. For any unexpected effects while taking MIRENA, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrm@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program
(CARDMP)
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.berlex.ca>

or by contacting the sponsor, Berlex Canada Inc., at:

1 800 361-0240

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