PRODUCT MONOGRAPH

PrMIRENA®

Levonorgestrel-releasing Intrauterine System (52 mg) to deliver

up to 20 mcg levonorgestrel per day

Progestogen

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PrMIRENA®

Levonorgestrel-releasing Intrauterine System

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intra-uterine	Intrauterine system / 52 mg levonorgestrel	barium sulphate, iron oxide, polydimethylsiloxane, polyethylene, silica *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

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

- conception control for maximum up to 5 years
- treatment of idiopathic menorrhagia following appropriate diagnostic investigation in women accepting the contraceptive effect of MIRENA

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

- known or suspected progestin-dependent neoplasia, including breast cancer
- cervicitis
- cervical dysplasia
- active liver disease or dysfunction
- actual benign or malignant liver tumors
- septic abortion within the previous three months
- hypersensitivity to levonorgestrel or any of the other ingredients in the formulation or 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

- Hormonal contraceptives **DO NOT PROTECT** against Sexually Transmitted Infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH MIRENA.**
- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke (see **Cardiovascular** section below).
- **Uterine Perforation may occur with the use of intrauterine contraceptives including MIRENA (see Uterine Perforation section).**

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 active or previous severe arterial disease such as stroke or myocardial infarction (see **WARNINGS AND PRECAUTIONS – Cardiovascular; Hematologic; Neurologic**). Removal of MIRENA should be considered if any of the above conditions occur during use.

Cases of breast cancer have been reported in users of MIRENA (see **WARNINGS AND PRECAUTIONS – Carcinogenesis and Mutagenesis**).

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

MIRENA is not suitable for use as a postcoital contraceptive.

Insertion Removal and Replacement Precautions

See **DOSAGE AND ADMINISTRATION** – **Insertion, Removal and Replacement** and **Insertion Instructions**.

Carcinogenesis and Mutagenesis

Breast Cancer

Cases of breast cancer have been reported in users of MIRENA (see **ADVERSE REACTIONS**).

The incidence rate of breast cancer in association with MIRENA use has been analyzed in a large Finnish epidemiological study using hospital registry data and cancer diagnoses derived from the Finnish Cancer Registry. In this study, the incidence rate of breast cancer in 17,360 MIRENA users (a total of > 58,000 women years with MIRENA, and > 150,000 women years of follow-up) was not statistically significantly different compared to the occurrence of breast cancer in 4,863 control women. In addition, the incidence rate of breast cancer among these MIRENA users has been compared to the average breast cancer incidence rates in Finland. There was no indication of a statistically significant difference between the MIRENA users and average Finnish female population in any of the age group of women studied (30-54 years). Although these studies do not support a causal relationship between MIRENA and the development of breast cancer, an elevated breast cancer risk cannot be totally excluded, since these studies did not control for confounding factors such as use of oral hormonal contraception by control subjects, genetics and lifestyle and environmental factors such as smoking and alcohol. (1, 2)

Increasing age, inherited mutations, and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include nulliparity, first full-term pregnancy after the age of 30, menarche before the age of 12, never breastfed a child, and daily alcohol consumption. In some women, the use of hormonal contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. More thorough studies are needed to determine the definitive link between hormonal contraceptive use and the potential risk of breast cancer. There is currently no conclusive evidence of an association between MIRENA use and development of breast cancer or progression of subclinical breast cancer. There is no reason to change prescribing habits at present.

Breast self-examination should be discussed with women receiving hormonal contraceptives. Women should be instructed to notify their healthcare professionals whenever any masses are detected.

Cardiovascular

An individual benefit-risk assessment in relation to continued use of MIRENA should be carried out in the event of arterial thrombosis. In particular, removal of MIRENA should be considered if severe arterial disease such as stroke or myocardial infarction occurs. In addition, MIRENA should be used with caution in patients with a previous history of severe arterial disease such as stroke or myocardial infarction. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence (see **WARNINGS AND PRECAUTIONS - Hematologic** and **Postmarket Adverse Drug Reactions**). There have been postmarket reports of cardiovascular events, including myocardial infarction and stroke in women using MIRENA, although a causal relationship with MIRENA could not be clearly established in these cases.

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Hormonal contraceptives increase this risk, especially with increasing age.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these risk factors.

Hypertension

If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during MIRENA use, MIRENA removal should be considered.

Congenital or Valvular Heart Disease

MIRENA should be used with caution in women with congenital or valvular heart disease who are at risk of infective endocarditis.

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. One published clinical study indicated no change in mean daily insulin requirements in women with Type 1 diabetes using MIRENA over a 12-month period. (3)

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 57% and 16% of users during the first year of use, respectively. Reduced bleeding increases the level of blood hemoglobin. Hemoglobin and serum ferritin levels have been shown to increase after insertion of MIRENA among women with anemia due to heavy menstrual bleeding. (4)

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

An individual benefit-risk assessment in relation to continued use of MIRENA should be carried out in the event of thrombosis. In particular, removal of MIRENA should be considered if venous thromboembolic disease such as deep vein thrombosis or pulmonary embolism occurs. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence (see **WARNINGS AND PRECAUTIONS – Cardiovascular** and **Postmarket Adverse Drug Reactions**). There have been postmarketing reports of arterial and venous thromboembolism (ATE, VTE) in women using MIRENA, although a causal relationship with MIRENA could not be clearly established in such cases. 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. (5-7)

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.

Other Risk Factors for Venous Thromboembolism

Other generalized risk factors for venous thromboembolism include but are not limited to a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index $\geq$30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, or trauma. Also patients with varicose veins and leg cast should be closely monitored.

Hepatic/Biliary/Pancreatic

Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal (see **CONTRAINDICATIONS**).

To date, no studies have examined whether the avoidance of the first-pass effect through the liver, as with non-oral hormonal contraceptives, lessens concerns in women with liver conditions. (8)

Jaundice

Patients who have had jaundice should be given hormonal contraceptives only with great care and under close observation. If jaundice develops in a patient using MIRENA, consideration should be given to removing the system. Hormonal contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. This condition may recur with subsequent hormonal contraceptive use (see **CONTRAINDICATIONS**).

Neurologic

Headache

MIRENA should be used with caution in women with a history of migraine headache, including migraine with focal neurological symptoms. The onset or exacerbation of migraine or the development of headaches with a new pattern that is recurrent, persistent or severe requires evaluation of the cause and consideration to remove MIRENA (see **WARNINGS AND PRECAUTIONS – General; Cardiovascular**).

Ophthalmologic

Contact Lenses

Any eye problems or discomfort occurring during use of a hormonal contraceptive, including those relating to the use of contact lenses, should be assessed. If this occurs, an ophthalmologist should be consulted. Temporary or permanent cessation of wear may be advised.

Peri-Operative Considerations

Thromboembolic Complications – Postsurgery

Women using MIRENA who require surgery associated with prolonged immobilization should be followed closely for signs and symptoms of thromboembolism.

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.

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.

Ovarian cysts have been reported as an adverse drug reaction in 6.8%-8.2% of women using MIRENA as a contraceptive (duration of use from 1 to 5 years), and in 5.5%-10.4% of women using MIRENA to treat menorrhagia (duration of use from 6 months to 5 years). In a large 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 cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the ovarian cysts 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. Carefully consider the possibility of an ectopic pregnancy in women who become pregnant while having MIRENA in place. Pregnancies with MIRENA use are rare, however, when a woman becomes pregnant with MIRENA in situ, the relative likelihood of ectopic pregnancy is increased. Up to half of the pregnancies that occur with MIRENA in place are ectopic. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain, especially in association with missed periods, or if an amenorrheic woman starts bleeding.

Women who choose MIRENA should be told about the risk of ectopic pregnancy, including the possibility of impaired fertility or loss of fertility. Educate women to recognize and report to their healthcare professional any signs and symptoms of ectopic pregnancy.

Combined data from prospective clinical trials with MIRENA reveal an overall rate of ectopic pregnancy of 0.06 per 100 woman-years. A similar ectopic pregnancy rate has been reported in a postmarketing surveillance study with data from over 17,000 women using MIRENA. (9) 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 per 100 woman-years.

Pelvic Infection

The inserter provided with MIRENA helps protect the system from contamination with micro-organisms during insertion, thereby minimizing the risk of pelvic infection. The exposed product should be handled with aseptic precautions (see **DOSAGE AND ADMINISTRATION – Insertion Instructions**). Known risk factors for pelvic inflammatory disease include multiple sexual partners, frequent intercourse and young age. Less common causes of pelvic inflammatory disease include pelvic actinomycosis and pelvic tuberculosis, both of which are extremely rare. There is an increased risk of PID during 20 days following the insertion of IUDs related to the insertion procedure. Thereafter, the risk of PID during the use of IUDs or MIRENA is small. Patients should be advised to report to their healthcare professionals promptly if they experience symptoms suggestive of PID. (10-12)

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.

Sepsis

There have been very rare postmarket reports of Group A streptococcal sepsis temporally associated with MIRENA insertion.

Uterine Perforation

Partial perforation (uterine embedment) or complete perforation of the uterus wall or cervix may occur during insertion, although the perforation may not be detected until later. Pregnancy may result from partial or complete perforation. If partial or complete perforation occurs, MIRENA must be located and removed; surgery may be required. Partial perforation (uterine embedment) can result in difficult removal. Delayed detection of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforation and obstruction, abscesses and erosion of adjacent viscera. The number of uterine perforations is linked to the experience of the person inserting the system. (13) Removal of a perforated IUS was associated (in a few cases) with sliding/separating of the hormone cylinder. During clinical trials with MIRENA, perforation occurred at a rate between 0.1 and 1 per 1000 insertions. These clinical trials excluded breast-feeding women.

In a large, prospective, comparative, non-interventional, cohort study (1 year follow-up period) in MIRENA and copper IUD users (N = 61,448 women), the incidence of perforation was 1.3 (95% CI: 1.1 - 1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1 - 1.8) per 1000 insertions in the MIRENA cohort and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women using MIRENA or copper IUD), the incidence of perforation detected at any time during the entire 5-year period was 2.0 (95% CI: 1.6 – 2.5) per 1000 insertions; 2.1 (95% CI: 1.6 – 2.8) and 1.6 (95% CI: 0.9 – 2.5) for MIRENA and copper IUD, respectively.

The study showed that both breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 2). These risk factors were confirmed in the subgroup followed up for 5 years. Both risk factors were independent of the type of IUD inserted.

Table 2: Incidence of perforation per 1000 insertions for the entire study cohort observed over 1 year, stratified by breastfeeding and time since delivery at insertion (parous women)

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=6047 insertions)	1.7 (95% CI 0.8-3.1; n=5927 insertions)
Insertion > 36 weeks after delivery	1.6 (95% CI 0.0-9.1; n=608 insertions)	0.7 (95% CI 0.5-1.1; n=41910 insertions)

The risk of perforation may be increased in women with abnormal uterine anatomy or with fixed retroverted uteri.

To reduce the possibility of perforation postpartum, MIRENA insertion should be delayed a minimum of 6 weeks after delivery or until uterine involution is complete. If involution is delayed, consider waiting until 12 weeks postpartum. Inserting MIRENA immediately after first trimester abortion is not known to increase the risk of perforation, but insertion after second trimester abortion should be delayed until uterine involution is complete.

To reduce the possibility of perforation, it is important to follow the recommended insertion technique (see **DOSAGE AND ADMINISTRATION – Insertion Instructions**).

Inform patients before the procedure about the risk of uterine perforation and educate them on possible signs of this complication, including, but not limited to, severe low abdominal pain, which may be associated with bleeding after the procedure, loss of threads, or change in thread length.

Uterine Embedment

Embedment of MIRENA in the myometrium may occur. Embedment may decrease contraceptive effectiveness and result in pregnancy. An embedded MIRENA must be removed. Embedment can result in difficult removal, and may require surgery.

Expulsion

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. 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 (see **DOSAGE AND ADMINISTRATION – Expulsion)**. A partially expelled MIRENA should be removed. A new system can be inserted at that time provided pregnancy has been excluded.

The risk of expulsion may be increased when the uterus is not completely involuted at the time of insertion. Delay MIRENA insertion a minimum of six weeks or until uterine involution is complete following a delivery or a second trimester abortion.

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

Special Populations

Pregnant Women/Intrauterine Pregnancy

The use of MIRENA during an existing or suspected pregnancy is contraindicated (see also **CONTRAINDICATIONS**). If pregnancy occurs with MIRENA in place, MIRENA should be removed 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. In the event of an intrauterine pregnancy with MIRENA in place, consider the following:

a) Risk of septic abortion

b) Continuation of pregnancy
If MIRENA cannot be removed or the woman chooses not to have it removed, she should be warned that failure to remove MIRENA increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Ectopic pregnancy should be excluded. The woman should be followed closely and advised to report any abnormal symptoms, such as fever, chill, cramping, abdominal pain, bleeding, vaginal discharge, or leakage of fluid.

c) Long-term effects and congenital anomalies
When pregnancy continues with MIRENA in place, long-term effects on the offspring are unknown. Congenital anomalies in live births have occurred infrequently. There have been few cases of masculinization of the external genitalia of the female fetus following local exposure to levonorgestrel during pregnancy with an LNG-IUS in place.

Nursing Women

Hormonal contraceptives are not recommended as the contraceptive method of first choice in breast-feeding women. A published study indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel could be transferred to the newborn via milk. (14) 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. However, isolated cases of decreased milk production have been reported with MIRENA.

Pediatrics (< 18 years of age)

Controlled clinical trials were done in previously parous women aged mainly over 18 years. Use of this product before menarche is not indicated.

Geriatrics

MIRENA is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before insertion, the woman must be informed of the efficacy, risks, and side effects of MIRENA. As well, before MIRENA is inserted, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active. Pregnancy and sexually transmitted infections should be excluded, and genital infections have to be successfully treated. For timing of insertion to exclude pregnancy see **DOSAGE AND ADMINISTRATION – Insertion, Removal and Replacement.**

Women should be re-examined 4 to 12 weeks after insertion and at least once a year thereafter, or more frequently if clinically indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on Preventive Health Care.

See also **DOSAGE AND ADMINISTRATION – Medical Examination/Consultation.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The majority of women experience changes in menstrual bleeding pattern after insertion of MIRENA (levonorgestrel-releasing intrauterine system [52 mg]). Over time, the frequency of amenorrhea and infrequent bleeding increases, and the frequency of prolonged, irregular and frequent bleeding decreases (see **WARNINGS AND PRECAUTIONS – Genitourinary**, ***Bleeding irregularities***; and **ACTION AND CLINICAL PHARMACOLOGY – *Pharmacodynamics***).
The serious adverse reactions of ectopic pregnancy, intrauterine pregnancy, sepsis. pelvic inflammatory disease, perforation, expulsion and ovarian cysts are discussed in **WARNINGS AND PRECAUTIONS**.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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.

Adverse drug reactions (ADRs) were collected from a total of 3,754 subjects using MIRENA during 9 clinical trials in contraception (n=3422) and 10 clinical trials in menorrhagia (n=332), worldwide. The length of treatment varied between studies: from 3 months to 5 years in the

MIRENA menorrhagia studies and from 1.5 months to 5 years in the MIRENA contraception studies.

ADRs were more common during the first months after insertion of MIRENA, and then gradually decreased over time. The ADR safety profile was consistent across the two indications.

Table 3: Number and Percentage of Subjects (≥1.0%) with Treatment-related AEs (ADRs) by Preferred Team[a] – FAS for all Contraception and Menorrhagia Studies with MIRENA

System Organ Class	N= 3754 Very Common (≥10%)	N= 3754 Common (≥1% to <10%)
Gastrointestinal disorders		Abdominal pain Nausea Pelvic pain
General disorders		Pain
Infections and infestations		Vaginal infection
Injury, poisoning, and procedural complications		Procedural pain
Investigations		Weight increased
Musculoskeletal and connective tissue disorders		Back pain
Nervous system disorders		Headache
Psychiatric disorders		Depression Libido decreased Nervousness
Reproductive system and breast disorders	Amenorrhea Hypomenorrhea Menstrual disorder Metrorrhagia	Breast pain Breast tenderness Dysmenorrhea Genital hemorrhage IUD complication Menometrorrhagia Menorrhagia Menstruation irregular Oligomenorrhea Ovarian cyst Polymenorrhea Vaginal/genital discharge
Skin and subcutaneous tissue disorders		Acne Skin disorder

a MedDRA Version 11.0 coding
N=total number of subjects;
Note: In original study reports causalities of related AEs are defined as 'Yes', 'Possible', 'Probable', or 'Certain'

Postmarket Adverse Drug Reactions

The most commonly occurring adverse events (ie, in greater than 10% of users) that are observed post marketing with MIRENA (levonorgestrel-releasing intrauterine system) are uterine/vaginal bleeding (including frequent, prolonged or heavy bleeding, spotting, oligomenorrhea, amenorrhea) and benign ovarian cysts.

In a large, prospective, comparative, non-interventional, cohort study (1 year follow-up period) in MIRENA and copper IUD users (N = 61,448 women), the incidence of perforation was 1.3

(95% CI: 1.1 - 1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1 - 1.8) per 1000 insertions in the MIRENA cohort and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. This study showed that breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth are independent risk factors for perforation (see **WARNINGS AND PRECAUTIONS – Sexual Function/Reproduction; Uterine Perforation)**.

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.

Table 4: Adverse Reactions Identified in Postmarketing Surveillance

Gastrointestinal disorders:	abdominal bloating
General disorders and administration site conditions:	expulsion, device breakage
Investigations:	blood pressure increased
Nervous system disorders	migraine
Reproductive system and breast disorders:	breast cancer, breast tension, mastalgia, pelvic pain, uterine perforation
Skin and subcutaneous disorders:	chloasma, hirsutism, alopecia, hypersensitivity including rash, pruritis, urticaria and angioedema

Device breakage has been reported with the use of MIRENA. This can occur with MIRENA in place or during its removal. The broken pieces should be located and removed; surgery may be required. Check device integrity when removing MIRENA.

Isolated postmarketing cases of decreased milk production have been reported in women using a LNG-IUS.

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

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

DRUG INTERACTIONS

Drug-Drug Interactions

No drug-drug interaction studies have been conducted with MIRENA.

The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes, specifically cytochrome P450 enzymes. 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.

Substances increasing the clearance of levonorgestrel

Substances which may increase the clearance of levonorgestrel include phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, and products containing St. John's wort.

Substances with variable effects on the clearance of levonorgestrel

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

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors)

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

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.

Tissue Specimens

Pathologists should be advised of MIRENA therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

Drug-Lifestyle Interactions

The effect of MIRENA on the ability to drive or to use machines has not been studied. Patients should be advised not to drive or use machines until they know how they react to MIRENA.

DOSAGE AND ADMINISTRATION

Recommended Dose

Following insertion into the uterine cavity, MIRENA (levonorgestrel-releasing intrauterine system) is effective for up to 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. Estimated in vivo release rates for different points in time are provided in Table 5.

Table 5: Estimated *in vivo* release rates

Time	Estimated *in vivo* release rate [micrograms/24 hours]
Initial	20
1 year after insertion	18
3 year after insertion	14
5 years after insertion	10
Average over 5 years	**15**

Administration

Medical Examination/Consultation

Before insertion, the patient must be informed of the efficacy, risks and side effects of MIRENA. A thorough history and physical examination should also be performed prior to insertion, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. Cervical smear (Papanicolaou smear) should be performed as needed, according to healthcare professional's evaluation. Pregnancy and sexually transmitted infections should be excluded and any genital infections must be successfully treated. For timing of insertion to exclude pregnancy see **DOSAGE AND ADMINISTRATION – Insertion, Removal and Replacement**. 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. Because irregular bleeding is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of MIRENA (see **WARNINGS AND PRECAUTIONS – Genitourinary**, ***Bleeding irregularities***; and **ADVERSE REACTIONS**). It is also important to counsel women about how their bleeding pattern may change after insertion of MIRENA. 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.

MIRENA is not suitable for use as a postcoital contraceptive.

Insertion, Removal and Replacement

In women of fertile age, MIRENA should be inserted within seven days of the onset of menstruation. In this case no back up contraception is needed. MIRENA can be inserted any time during the cycle if the healthcare professional can be reasonably certain (as defined by the World Health Organization) that the woman is not pregnant. If insertion is more than seven days since menstrual bleeding started, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for the next seven days to prevent pregnancy. Consider the possibility of ovulation and conception before using this product. 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.

Insertions following second trimester abortion should be postponed for a minimum of 6 weeks or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion.

Postpartum insertions should be postponed until the uterus is fully involuted, and not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be undertaken.

MIRENA can be removed by applying gentle traction on the threads with forceps. If the threads are not visible, determine the location of MIRENA by ultrasound. If MIRENA is found in the uterine cavity, it may be removed using forceps. This may require dilatation of the cervical canal or other surgical intervention, such as hysteroscopy. After removal of MIRENA, verify that the system is intact.

During difficult removals (ie, removal through a tight cervical canal or surgical removal after perforation), the hormone cylinder may slide over and cover the horizontal arms. This situation generally does not require further intervention once the system is verified to be intact. The reporting rate for hormone cylinder dislocation/shifting with MIRENA is approximately 7 per 1 million insertions.

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 within 7 days of the onset of menstruation in women of fertile age provided the woman is experiencing regular menses.

If the system is removed at some other time or the woman does not experience regular menses and the woman has had intercourse within a week, she is at risk of pregnancy unless a new system is inserted immediately following removal. If MIRENA will not be replaced, the patient should consider starting a new contraceptive method a week prior to 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. It is recommended to wait 24 to 48 hours before having sexual intercourse in the event of general discomfort after insertion of MIRENA.

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 threads are not visible upon follow-up examination, they may have retracted into the uterus or broken, or MIRENA may have broken, perforated the uterus, or been expelled. If the length of the threads has changed from the length at the time of insertion, the system may have become displaced (see **DOSAGE AND ADMINISTRATION - Administration; Expulsion**). Pregnancy must be excluded and the location of MIRENA must be verified by sonography, X-ray (MIRENA is radiopaque), or by gentle exploration of the uterine cavity with a probe. If MIRENA is displaced, remove it. A new MIRENA may be inserted at that time or during the next menses if it is certain that conception has not occurred.

Missed Dose

MIRENA should be removed after 5 years. If the user wishes to continue using MIRENA, a new system can be inserted replacing the old system. If the system has been used for a longer period of time than 5 years, pregnancy should be ruled out before insertion of a new system.

Overdose

Not applicable. MIRENA is an intrauterine system.

Insertion Instructions

Before insertion, the patient must be informed of the efficacy, risks and side effects of MIRENA.

Because the insertion technique is different from other intrauterine devices, it is important that health care professionals receive training on the correct insertion technique.

Health care professionals should become thoroughly familiar with the insertion instructions in their entirety before insertion of MIRENA

MIRENA is supplied in a sterile package which should not be opened until required for insertion. MIRENA is sterilized with ethylene oxide. Do not resterilize. MIRENA is for single use only. Do not use if the seal of the sterile package is broken, or if the package is damaged or opened.

The exposed product should be handled with aseptic precautions. Insert MIRENA before the expiry date indicated on the label.

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

In women of fertile age, MIRENA is inserted into the uterine cavity using the enclosed inserter within seven days of the onset of menstruation by carefully following these insertion instructions (Figure 1). In this case no back up contraception is needed. MIRENA can be inserted any time during the cycle if the healthcare professional can be reasonably certain (as defined by the World Health Organization) that the woman is not pregnant. If insertion is more than seven days since menstrual bleeding started, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for the next seven days to prevent pregnancy. Consider the possibility of ovulation and conception before using this product. MIRENA is not suitable for use as postcoital contraceptive. It can be replaced by a new system at any time during the menstrual cycle. For additional information on the timing of insertion, please see the **DOSAGE AND ADMINISTRATION**, **Administration, Insertion, Removal and Replacement** subsection of the Product Monograph.

A physical examination including pelvic examination, examination of the breasts and cervical smear should be performed prior to insertion. 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 with the aid of a speculum and thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
2. Grasp the upper lip of the cervix with a tenaculum or suitable holding forceps to stabilize the uterus. If the uterus is retroverted, it may be more appropriate to grasp the lower lip of the cervix. Gentle traction on the holding forceps can be applied to straighten the cervical canal. The forceps should remain in position and gentle traction on the cervix should be maintained throughout the insertion procedure.
3. Gently advance a uterine sound through the cervical canal to the fundus to determine the depth and confirm the direction of the uterine cavity, and to exclude any evidence of intrauterine abnormalities (eg, uterine septum, synechiae or submucosal fibroids) or a previously inserted intrauterine contraceptive which has not been removed. If difficulty is encountered, consider dilatation of the canal. If cervical dilatation is required, consider using analgesics and/or paracervical block.

Insertion

Step 1–Opening of the sterile package

- First, open the sterile package completely (Figure 1). Then use aseptic technique and sterile gloves.

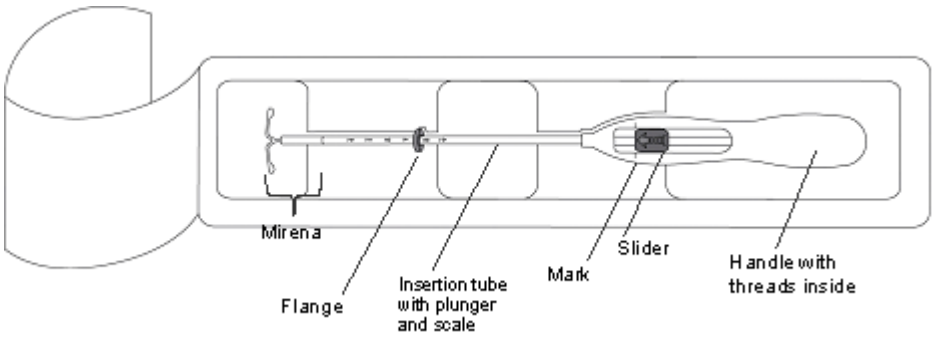


Figure 1: Sterile Package Containing MIRENA

Step 2–Load MIRENA into the insertion tube

- To load MIRENA into the insertion tube, push the slider **forward** in the direction of the arrow to the furthest position (Figure 2).

- IMPORTANT! Do not pull the slider downwards as this may prematurely release MIRENA. **Once released, MIRENA cannot be re-loaded.**

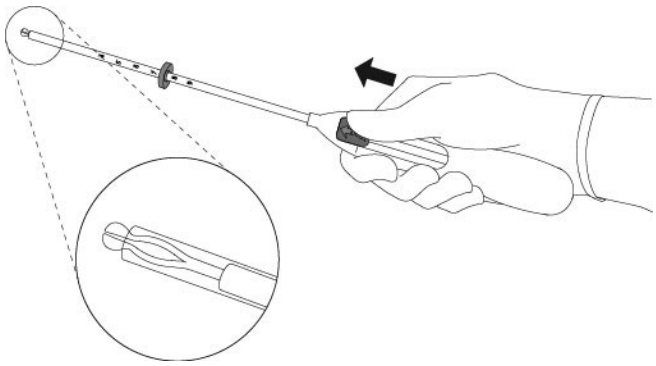


Figure 2: Loading MIRENA into the Insertion Tube

Step 3–Setting the flange

- Holding the slider in the furthest position, set the **upper** edge of the flange to correspond to the sound measurement of the uterine depth (Figure 3).

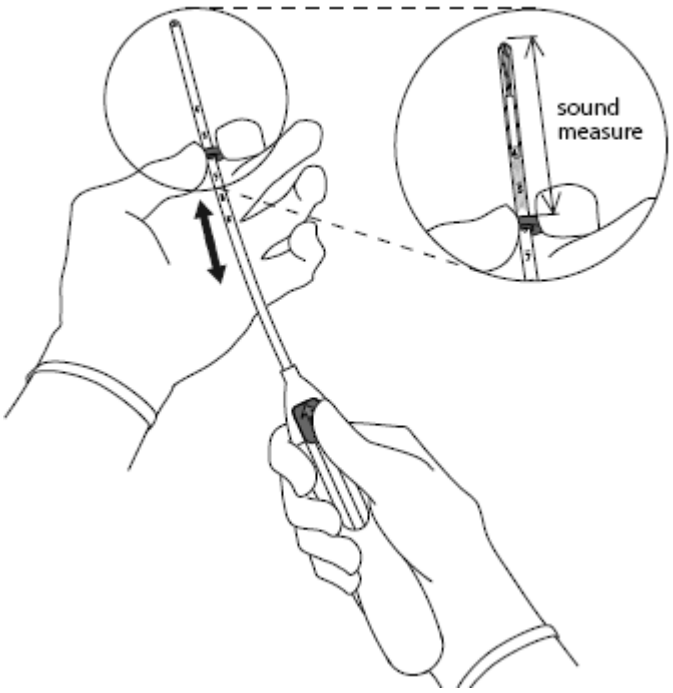


Figure 3: Setting the Flange to the Uterine Depth

Step 4–MIRENA is now ready to be inserted

- While holding the slider in the **furthest** position, gently advance the inserter through the cervical canal and into the uterine cavity **until the flange is approximately 1.5 to 2.0 cm from the external cervical os** (Figure 4).
- **NOTE: Do not advance flange to the cervix at this step.** Maintaining the flange 1.5 to 2 cm from the cervical os allows sufficient space for the arms to open (when released) within the uterine cavity.
- **IMPORTANT! Do not force the inserter. If necessary, dilate the cervical canal.**

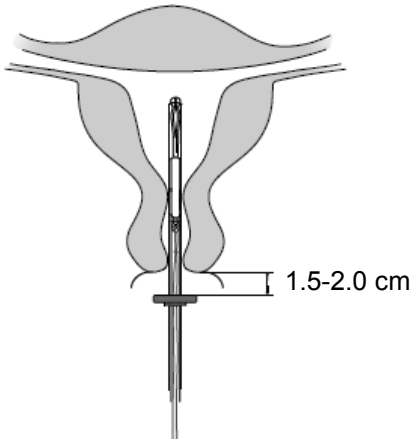


Figure 4: Advancing the Inserter Until Flange is 1.5 to 2 cm From Cervical Os

Step 5–Release the arms

- While holding the inserter steady, **pull the slider to the mark** to open the horizontal arms of MIRENA (Figure 5). Wait approximately 10 seconds for the horizontal arms of MIRENA to open completely.

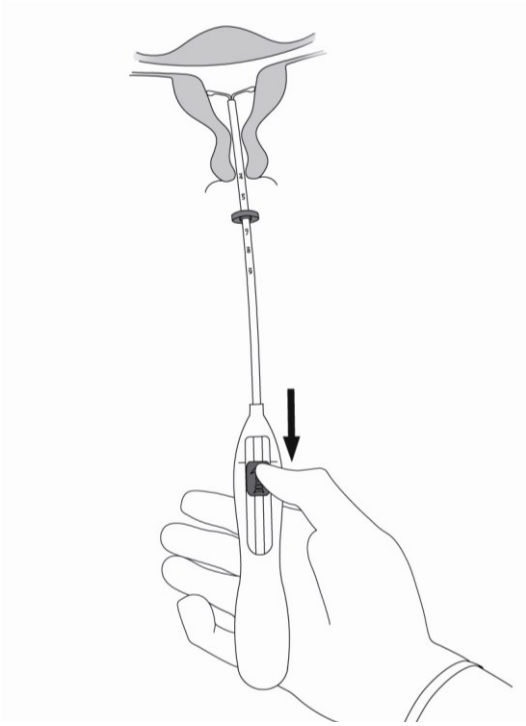


Figure 5: Releasing the Arms of MIRENA

Step 6–Advance to fundal position

- Advance the inserter gently towards the fundus of the uterus **until the flange touches the cervix** or you feel fundal resistance. MIRENA should now be in the desired fundal position (Figure 6).

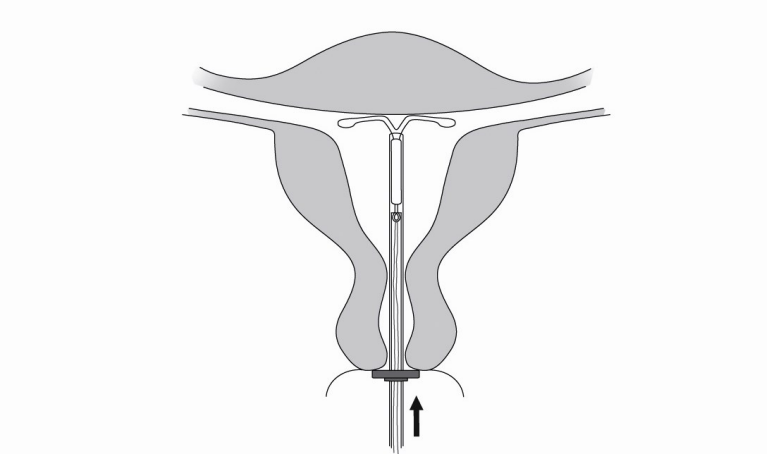


Figure 6: MIRENA in the Fundal Position

Step 7–Release MIRENA and withdraw the inserter

- While holding the inserter in place, pull **the slider all the way down** to release MIRENA from the insertion tube (Figure 7). The threads will release automatically from the internal thread lock of the inserter.
- Gently remove the inserter by pulling it out.
- **Cut the threads perpendicular** to the thread length, for example, with sterile curved scissors, leaving about 2-3 cm visible outside of the cervix. NOTE: Cutting the threads at an angle may leave sharp ends.

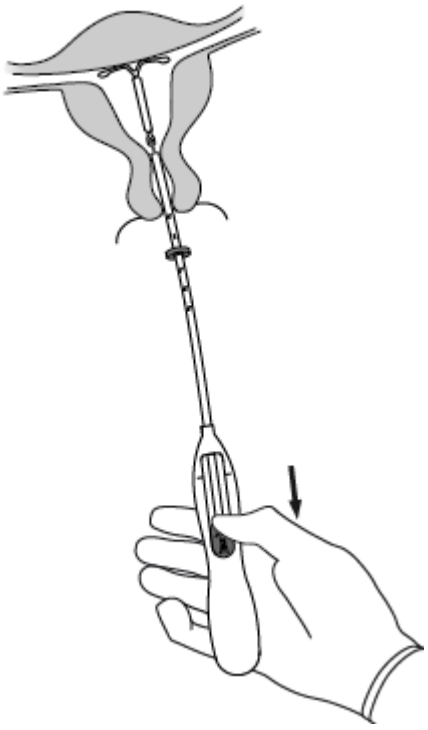


Figure 7: Releasing MIRENA from the Insertion Tube

MIRENA insertion is now complete.

IMPORTANT!

If you suspect that MIRENA is not in the correct position, check placement (for example, with transvaginal ultrasound). Remove the system if it is not positioned properly within the uterine cavity. A removed system must not be re-inserted.

If there is clinical concern and/or exceptional pain or bleeding during or after insertion, appropriate and timely measures and assessments, for example ultrasound, should be performed to exclude perforation.

Patients should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Use of Sanitary Pads or Menstrual Cups

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

Removal/Replacement of MIRENA

Timing of Removal

- MIRENA should not remain in the uterus after 5 years.
- If pregnancy is not desired, the removal should be carried out during menstruation, provided the woman is still experiencing regular menses. If removal will occur at other times during the cycle, consider starting a new contraceptive method a week prior to removal. If removal occurs at other times during the cycle and the woman has had intercourse in the week prior to removal, she is at risk of pregnancy.

Tools for Removal

Preparation

- Gloves
- Speculum

Procedure

- Sterile forceps

Removal Procedure

- Remove MIRENA by applying gentle traction on the threads with forceps (Figure 8).
- If the threads are not visible, determine location of MIRENA by ultrasound.
- If MIRENA is found to be in the uterine cavity on ultrasound exam, it may be removed using a narrow forceps, such as an alligator forceps. This may require dilation of the cervical canal. After removal of MIRENA, examine the system to ensure that it is intact.

Removal may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, or a seizure in an epileptic patient).

Replacement

If after 5 years, continued use of MIRENA is desired, a new MIRENA should be inserted immediately after the old one is removed. A replacement MIRENA can be inserted at any time during the menstrual cycle.

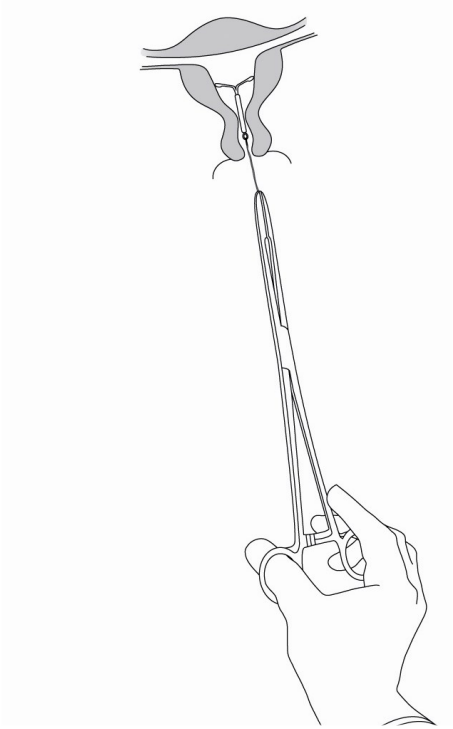


Figure 8: Removal of MIRENA

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. MIRENA is a long acting reversible contraceptive (LARC). 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 mcg per day that diminishes over time to approximately 10 mcg per day after 5 years. MIRENA does not contain any estrogen.

polyethylene T-shaped frame

cylindrical reservoir containing levonorgestrel

polyethylene removal threads

Figure 9: 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 5 years of use in clinical trials, the return of normal cyclical endometrial morphology was observed to occur from 1 to 3 months after removal of MIRENA. The use of MIRENA does not alter the course of future fertility; upon removal of MIRENA, women return to their normal fertility. Women requesting the removal of MIRENA for reasons of planning a pregnancy were followed for 24 months. During the 24-month period, nearly 90% of these women were able to get pregnant. (16)

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.

During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after postmenstrual insertion of MIRENA, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, amenorrhea is experienced by 0% and infrequent bleeding by 11% during the first 90 days, increasing to 16% and 57% at the end of the first year of use, respectively (Table 6) (15). Reduced bleeding has been shown to increase the level of blood hemoglobin and ferritin in women who have anemia from heavy menstrual bleeding (4).

Table 6: Percentage of subjects meeting the criteria for different patterns of bleeding during the first 90 days and at the End of Year 1		
MIRENA	**First 90 days**	**End of year 1**
Amenorrhea	0 %	16 %
Infrequent bleeding	11 %	57 %
Frequent bleeding	13 %	1 %
Prolonged bleeding	22 %	3 %
Irregular bleeding	67 %	19 %

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 7).

Table 7: 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 preovulatory 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 mcg/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 multicentre 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. More than 90% of the released levonorgestrel is systemically available.

After insertion of MIRENA, levonorgestrel is detectable in serum after 1 hour. The maximum concentration is reached within 2 weeks after insertion. Following intrauterine insertion of MIRENA, the initial release rate of levonorgestrel is 20 mcg per day. In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 pg/ml (25th to 75th percentiles: 151 pg/ml to 264 pg/ml) at 6 months to 194 pg/ml (146 pg/ml to 266 pg/ml) at 12 months, and to 131 pg/ml (113 pg/ml to 161 pg/ml) at 60 months in women of reproductive age weighing above 55 kg. Because of the low drug levels in plasma, the systemic effects of the progestogen are minimized.

Distribution

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. Less than 2% of the total serum drug levels are present as free steroid. Levonorgestrel binds with high affinity to SHBG. Accordingly, changes in the concentration of SHBG in serum result in an increase (at higher SHBG concentrations) or in a decrease (at lower SHBG concentrations) of the total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 20-30% during the first month after insertion of MIRENA, remained stable during the first year and increased slightly thereafter. For levonorgestrel, the mean apparent volume of distribution is about 106 L.

Metabolism and Excretion

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

The terminal half-life in serum is in the range of 14 to 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. A published study indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel could be transferred to the newborn via milk. (14)

Special Populations and Conditions

Pediatrics (< 18 years of age)

Controlled clinical trials were done in previously parous women aged mainly over 18 years. Use of this product before menarche is not indicated.

Geriatrics

MIRENA is not indicated for use in postmenopausal women.

Hepatic Insufficiency

MIRENA is contraindicated in women with acute liver disease or liver tumors (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**)

Renal Insufficiency

MIRENA has not been studied in women with renal impairment.

STORAGE AND STABILITY

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

Keep out of reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

MIRENA (levonorgestrel-releasing intrauterine system) should be handled with aseptic precautions. Used MIRENA systems should be considered biohazardous waste and disposed of accordingly. Care should be taken to ensure the remaining hormonal ingredients are not introduced into water/sewer systems.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each MIRENA (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel 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 white T-frame is pigmented with barium sulphate, which makes it visible in X-ray examination. Brown polyethylene removal threads attached to the T-frame are pigmented with black iron oxide.

MIRENA is in a sterile package within the EvoInserter. The EvoInserter, which is used for insertion of MIRENA into the uterine cavity, consists of a symmetric two-sided body and slider that are integrated with flange, lock, insertion tube and plunger. The outer diameter of the insertion tube is 4.4 mm. The vertical stem of MIRENA is loaded in the insertion tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once MIRENA has been placed, the inserter is discarded.

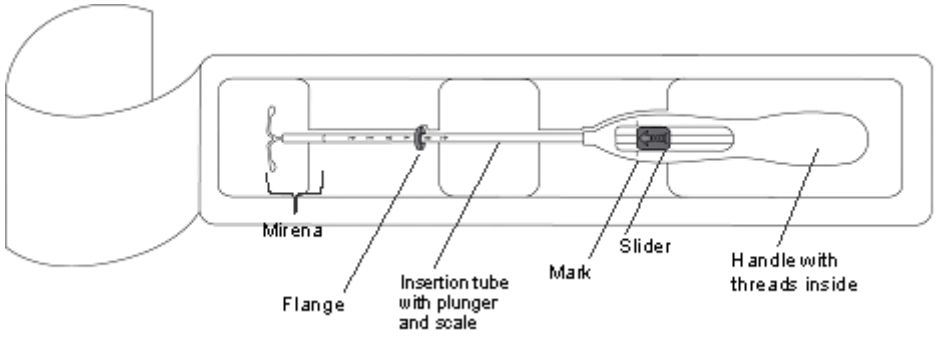


Figure 10: MIRENA EvoInserter

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

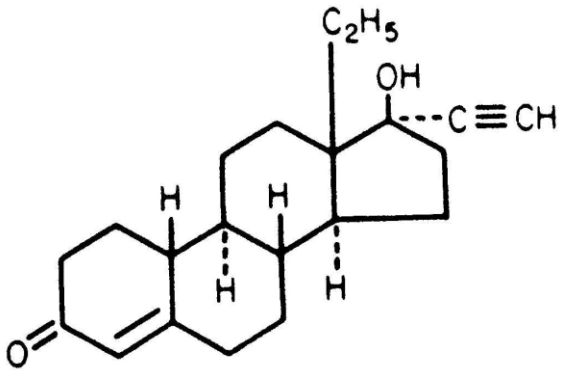
Proper name: levonorgestrel

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

Molecular formula: C_{21} H_{28} O_2

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

Contraception

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 (zero). A third MIRENA trial was noncomparative, 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 Index of 0.11, representing approximately 99.9% efficacy.

Treatment of Idiopathic Menorrhagia

The pivotal menorrhagia study was a prospective, randomized, active-controlled, multicenter study in subjects randomized to MIRENA or medroxyprogesterone acetate (MPA; 10 mg given orally, once daily for 10 consecutive days starting on the 16th day of each menstrual cycle) over 6 cycles. Women with a normal length of menstrual cycle consisting of 21 to 35 days and withdrawal bleeding with menstrual blood loss (MBL) ≥80 mL measured at baseline were included in the study. Efficacy of both treatments was demonstrated using the objective alkaline hematin method for measuring MBL. The primary efficacy variables were the absolute change in MBL from baseline to the end-of-study and the proportion of subjects with successful treatment. Successful treatment was defined as end-of-study MBL < 80 mL and a decrease in value of ≥ 50% of baseline MBL.

Table 8: Summary of Patient Demographics in Menorrhagia Pivotal Trial

Study Number	Trial Design	Study Drug	Duration	No. of Subjects[a]	Mean Age years (range)
309849 (17)	Open-label, randomized, multicenter, parallel	Test product: MIRENA 52 mg (20 mcg/24 hrs)	6 cycles	N=82	38.3 (26 – 50)
		Comparator: Medroxyprogesterone acetate 10 mg po od administered for 10 consecutive days beginning on the 16th day of the menstrual cycle	6 cycles	N=83	39.3 (26 – 53)

No.=number; od=once daily; po=oral administration
a FAS=full analysis set

MIRENA was found to be superior to MPA for reductions in median MBL from baseline to end-of-study (P<0.001) (see Table 9). The proportion of subjects who achieved successful treatment was also statistically and clinically significant in favor of the MIRENA treatment group (see Table 10).

Table 9: MIRENA vs MPA, The Absolute Change in MBL from Baseline to End-of-Study - Study 309849, FAS

Treatment Group	N	Median Baseline MBL (mL) [range]	Median End-of-Study MBL (mL) [range]	Change from Baseline to End-of-Study (mL) [range]	*P*-value[a] Between Treatment Groups
MIRENA	79	147.96 [68.3 to 431.4]	7.10 [0.0 to 1435.6]	-128.78 [-393.6 to 1242.2[b]]	$P < 0.001$
MPA	81	154.20 [63.4 to 456.0]	121.47 [0.0 to 437.7]	-17.77 [-271.5 to 78.6]	

FAS=full analysis set; MPA = medroxyprogesterone acetate tablets; N=number of subjects; primary analysis set for efficacy
a Statistical test: Wilcoxan-test. Significance level of the statistical test is 0.05 (two-sided).
b One subject experienced heavy blood loss thought to have resulted from the expulsion of MIRENA.

Table 10: MIRENA vs MPA, The Proportion of Subjects with Successful Treatment[a] - Study 309849, FAS

Assessement	MIRENA N=82 (n) [%]	MPA N=83 (n) [%]	% Difference between treatment groups	95% CI	*P*-value[b] Between Treatment Groups
Successful Treatment	67 (84.8%)	18 (22.2%)	62.59	50.56 – 74.61	P < 0.001
End-of-Study MBL < 80 mL	71 (87.7%)	24 (29.6%)	58.02	45.77 – 70.28	P < 0.001
Decrease in End-of-Study MBL > 50% of Baseline MBL	67 (84.8%)	22 (27.2%)	57.65	45.14	P < 0.001

CI=confidence interval; FAS=full analysis set, primary analysis set for efficacy; MPA=medroxyprogesterone acetate tablets; N=number of subjects

a Successful treatment is defined as: End-of Study MBL < 80 mL and decrease in End-of-Study MBL > 50% of Baseline MBL

b Statistical test: Pearson's Chi-squared test. Significance level of the statistical test is 0.05 (two-sided).

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).

General Information

The following table gives typical pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant within the first year of use.

Table 10: Reported Pregnancies per 100 Women Within the First Year of Use

Hormonal Intrauterine system (IUS)	less than 1
Copper Intrauterine device (IUD)	less than 1
Progesterone Injection	6
Combined hormonal contraceptive (pill, patch or ring)	9
Diaphragm	12
Male condom	18
Female condom	21
Sponge, spermicide	12-28
Withdrawal method	22
Natural family planning	24
No method	85

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 mcg/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 mcg/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 antiestrogenic 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 nonaqueous 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 nonaqueous 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 mcg 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 mcg 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.

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PART III: CONSUMER INFORMATION

PrMIRENA®

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 healthcare professional or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- to prevent pregnancy for up to 5 years
- the treatment of heavy menstrual bleeding without a known reason in women who are able to use a hormonal contraceptive method and have achieved menarche. Your first menstrual period is referred to as menarche.

What it does:

MIRENA is an intrauterine system (IUS). 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 amount of levonorgestrel:

- reduces the normal monthly thickening of the lining of the uterus.
- thickening the mucus in the cervix (this makes it harder for sperm to pass through the cervix), and
- Impairing sperm movement and function

Together, these actions prevent the sperm and egg from coming into contact and work together to prevent pregnancy.

These effects of levonorgestrel also decrease abnormally heavy menstrual blood loss.

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

MIRENA does not contain any estrogen.

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.

MIRENA is a long acting reversible contraceptive (LARC). LARCs are highly effective in preventing pregnancy. They can be used for a long period of time and are easy to use.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. When used properly, other methods of birth control are effective enough for many women.

The following table gives typical pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant within the first year of use.

Reported Pregnancies per 100 Women Within the First Year of Use

Hormonal Intrauterine system (IUS)	less than 1
Copper Intrauterine device (IUD)	less than 1
Progesterone Injection	6
Combined hormonal contraceptive (pill, patch or ring)	9
Diaphragm	12
Male condom	18
Female condom	21
Sponge, spermicide	12-28
Withdrawal method	22
Natural family planning	24
No birth control	85

The pregnancy rates listed in the table vary widely. This is because of differences in how carefully and regularly people use each method of birth control. Regular users may have lower pregnancy rates. Others may expect pregnancy rates in the middle ranges. This does not apply to IUDs because they are placed in the uterus and do not depend on user compliance.

When it should not be used:

MIRENA is not suitable for every woman. In a small number of women, serious side effects may occur. Your healthcare professional can advise you if you have any conditions that would pose a risk to you. The use of MIRENA should always be supervised by your healthcare professional. You should not use MIRENA if you:

- have any allergies to the hormone levonorgestrel, or to any of the other ingredients of MIRENA, or to components of the container (see the sections in this leaflet titled "What the medicinal ingredient is" and "What the nonmedicinal ingredients are")
- are pregnant, or if you suspect that you may be pregnant

- currently have pelvic inflammatory disease (PID) or have had recurrent PID (see the paragraph in this leaflet titled "Infections")
- have an infection of your lower genital tract
- had an infection of the uterus (womb) after delivering a baby
- have bleeding from the vagina that has not been explained
- have a condition of the uterus that distorts the uterine cavity, such as large fibroids
- have an infection of the cervix (neck of the womb)
- have cell abnormalities in the cervix (your healthcare professional can tell you if you have this)
- have a known or suspected progestogen-dependent tumor, including breast cancer
- have liver disease or liver tumor
- have had an infection of the uterus (womb) after having an abortion during the past 3 months
- have bacterial endocarditis (an infection of the heart valves or lining of the heart)
- have immunodeficiency (a healthcare professional will have told you if you have this)
- have cancer affecting the blood, or if you have leukemia
- have or have had trophoblastic disease (a healthcare professional will have told you if you have this)
- have cancer of the uterus or the cervix (uterine or cervical malignancy)

What the medicinal ingredient is:

levonorgestrel

What the nonmedicinal ingredients are:

barium sulphate, black iron oxide, polydimethysiloxane, polyethylene, silica.

What dosage form it comes in:

Each MIRENA (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel to deliver up to 20 mcg levonorgestrel per day for 5 years, and is enclosed in a package with the EvoInserter.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hormonal Contraceptives including MIRENA DO NOT PROTECT against Sexually Transmitted Infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms while using MIRENA.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. Women should be counseled not to smoke.

MIRENA may penetrate or perforate (punch a hole in) the wall of the uterus.

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

- are breast-feeding
- have given birth in the last 36 weeks
- have ever had an ectopic pregnancy (development of a fertilized egg outside the uterus). Ectopic pregnancy is more likely if you accidentally become pregnant while using MIRENA.
- have had surgery on your fallopian tubes.
- have a history of ovarian cysts. There is an increased risk of cysts on the ovary.
- have an unusual menstrual bleeding pattern.
- have an unusual or unpleasant (eg, 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 skin, whites of the eyes and/or nails)
- are diabetic or have a family history of diabetes, have high blood pressure or abnormal blood lipid levels
- have a history of blood clots (thrombosis)
- 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
- smoke

You should also inform your healthcare professional about a family history of blood clots, heart attacks, or strokes.

Women who had never given birth to a child or were less than 18 years of age were not included in controlled trials using MIRENA.

If you see a different healthcare professional, inform him or her that you are using MIRENA.

Tell your healthcare professional if you are scheduled for any laboratory tests, since certain tests may be affected by hormonal contraceptives. Also, tell your healthcare professional if you are scheduled for surgery requiring prolonged bed rest.

MIRENA should be used only under the supervision of a healthcare professional, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your healthcare professional 4 to 12 weeks after the initial examination. Afterward, visit your healthcare professional at least once a year. Use MIRENA only on the advice of your healthcare professional and carefully follow all directions given to you. Otherwise, you may become pregnant.

If you and your healthcare professional decide that, for you, the benefits of MIRENA outweigh the risks, you should be aware of the following:

The Risks of Using MIRENA

1. Circulatory Disorder (including blood clot in legs, lungs, heart, eyes, or brain)

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 healthcare professional.

Be alert for the following symptoms and signs of serious adverse effects. Call your healthcare professional immediately if they occur:

- Sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- Pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- Crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- Sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

2. Breast Cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include onset of menstrual periods before age 12 years, never having children, having your first full-term pregnancy after the age of 30 years, never having breast fed a child, and daily alcohol consumption.

Some studies have shown that the risk of developing breast cancer does not appear to be increased by using progestogen-only forms of birth control like MIRENA. However, more thorough studies are needed to confirm that there is no increased risk. You should notify your healthcare professional if you notice any breast lumps. You should also discuss breast self-examination with your healthcare professional. A yearly breast examination by a health care professional is recommended for all women.

3. Diabetes

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

4. Infections

There is an increased risk of a serious pelvic infection called pelvic inflammatory disease (PID) in the first three weeks after placement of an intrauterine system or device. Other known risk factors include multiple sexual partners, frequent intercourse, and young age. 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 healthcare professional 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.

5. Ectopic Pregnancy

Ectopic pregnancy (development of a fertilized egg outside the uterus) is possible when using MIRENA, as it is in women using no contraception. However, if you accidentally become pregnant while using MIRENA, an ectopic pregnancy is more likely. Ectopic pregnancy is a serious condition. Therefore, you should tell your healthcare professional if you have lower abdominal pain, especially if you have missed a period and/or have unexpected bleeding, since these can be signs of an ectopic pregnancy.

6. Cysts on the Ovary

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

7. Uterine Perforations

MIRENA may become attached to or go through the wall of the uterus. This is called perforation and it happens most often during placement. Perforation is uncommon. If this happens, MIRENA must be removed.

The risk of perforation is higher in women who are breastfeeding at the time of MIRENA placement and/or when MIRENA is placed up to 36 weeks after a delivery. The risk of perforation may be increased in women with an abnormally shaped uterus or with the uterus fixed and leaning backwards.

8. Use While Breast Feeding

Hormonal contraceptives are not recommended as a birth control method of first choice in women who are breast feeding. 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. Levonorgestrel does not appear to affect the amount or the quality of breast milk. You can use MIRENA during breast feeding. However, isolated cases of decreased milk production have been reported among women using MIRENA.

9. Use in Pregnancy

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 increase. The effect of levonorgestrel on a developing infant is not well known, and therefore, a detrimental effect cannot be completely ruled out. Removal of MIRENA or probing of the uterus may result in spontaneous abortion. If MIRENA cannot be removed, you should check with your healthcare professional about the benefits and risks of continuing the pregnancy, and possible effects to your unborn child.

10. Use After Pregnancy and Abortion

Following childbirth, MIRENA should be placed only after the womb has returned to its normal size, and not earlier than 6 weeks after delivery.

MIRENA can be placed immediately after a first trimester abortion. If an abortion takes place in the second trimester, placement of MIRENA should be delayed for 6 weeks or until the uterus has returned to normal size.

11. Pregnancy After Stopping MIRENA

If you wish to become pregnant, ask your healthcare professional to remove MIRENA. Your usual level of fertility should return soon after the system is removed. Nearly 90% of women wishing to become pregnant conceive within 24 months after removal of the system.

12. Broken MIRENA

MIRENA may break, most often during a difficult removal. Broken pieces must be found and removed. Surgery may be needed to do this.

Driving or Using Machines

The effect of MIRENA on the ability to drive or to use machines has not been studied. Do not drive or use machines until you know how you react to MIRENA.

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 MIRENA is removed, periods should return to normal.

What if I Stop Having Periods?

Over time, your menstrual period may gradually disappear when using MIRENA. 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.

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 healthcare professional.

INTERACTIONS WITH THIS MEDICATION

Please inform your healthcare professional 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 the hormone 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 brown coloured fine plastic threads are attached to the tip of the vertical arm. These threads are intended to be used for removal of MIRENA and also serve to check its presence once it is in place.

How is MIRENA Placed?

Before MIRENA is placed, you will have a pelvic examination to determine the position and size of your uterus. Your healthcare professional will place 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 healthcare professional will withdraw the tube leaving the system in place in the uterus. Finally, your healthcare professional will trim the removal threads to a suitable length.

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

Most women find that the placement 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 healthcare professional. Some women may feel faint after MIRENA is placed, but this feeling subsides after a short rest. The placement procedure may precipitate a seizure in epileptic patients.

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

When Should MIRENA be Placed?

MIRENA should be placed within seven days of starting your period. In this case, no back up birth control is needed. If it is certain that you are not pregnant, MIRENA may also be placed at any other time during your cycle. Tell your healthcare professional if you have had unprotected sex since your last period. If MIRENA is placed more than 7 days since your period started, use a condom or diaphragm, or do not have sex for the next 7 days. MIRENA cannot be used as emergency birth control. When replacing an existing system for a new one, it is not necessary to wait for your period.

How Long Does Placement Take?

The placement procedure usually takes a few minutes after your healthcare professional has completed the pelvic examination.

How Quickly Does MIRENA Start to Work?

MIRENA starts to work right away if it is placed within 7 days of the start of your period. It is best to wait 24-48 hours before having intercourse in case of discomfort. If MIRENA is placed more than 7 days after the start of your period, use a condom or diaphragm for the next 7 days. Alternatively, do not have sex for the next 7 days.

A reduction in menstrual blood loss should be apparent from the first menstrual cycle.

How Often Should I Have MIRENA Checked?

You should have MIRENA checked approximately 4 to 12 weeks after it is placed, 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 receive a patient reminder card from your healthcare professional after the placement of MIRENA. Keep this card until MIRENA is removed and bring it with you to every medical appointment.

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 healthcare professional will show you how to do this. Do not pull on the threads as you may accidentally pull MIRENA out.

If you cannot feel the threads, this may indicate that MIRENA has fallen out or uterine perforation has occurred. See your healthcare professional and in the meantime use another method of nonhormonal contraception. You should also see your healthcare professional if you can feel the lower end of MIRENA itself.

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 healthcare professional to verify it is still in the correct position.

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

Can Tampons or Menstrual Cups be Used?

Use of sanitary pads is recommended. If tampons or menstrual cups 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.

If you think it has come out, avoid intercourse or use another method of nonhormonal contraception until you see your healthcare professional.

Removal of MIRENA

MIRENA should not be left in place for more than 5 years. You should see your healthcare professional when you want to have MIRENA taken out. Removal of MIRENA is usually very easy. However, you should be aware that you may become pregnant upon removal of MIRENA if you have had sexual intercourse during the previous week.

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

Missed Dose

If you wish to continue using MIRENA after 5 years, your healthcare professional can place a new system after removing the old system. If the same MIRENA system has been left in place for longer than 5 years, you may become pregnant. Pregnancy should be ruled out before placement of a new system.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects with MIRENA are more common during the first months after placement; they gradually decrease over time.

Menstrual bleeding irregularities are the most common side effects of MIRENA during the first months after the system is placed, but these effects should decrease over time. Other common side effects might include abdominal pain and absence of menstruation.

The following side effects have also been observed in studies of women taking MIRENA:

Breast pain, IUD complication, pain, painful periods, altered mood, headache, acne, genital discharge, back pain, withdrawal bleeding, ovarian cyst, decreased sex drive, weight increase, menorrhagia, depression, vaginal infection, nervousness, nausea, vaginal hemorrhage, skin disorder.

Side effects of unknown frequencies include: device breakage.

Few women using MIRENA after delivery have reported less milk production.

Side effects such as irregular menstrual bleeding and nausea should go away as your body adjusts to MIRENA. If these symptoms do not go away or if you think you are reacting poorly to MIRENA or having other problems which are not listed above, please tell your healthcare professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM				
Symptom / possible side effect		**Talk with your healthcare professional or pharmacist**		**Get immediate medical help**
		Only if severe	**In all cases**	
Common	Vaginal bleeding	✓		
	Symptoms of vaginal infection, such as itching, or unusual or increased vaginal discharge		✓	
	Headache	✓		
	Abdominal pain		✓	
	Pelvic or back pain		✓	
	Feeling depressed or nervous		✓	
	Expulsion of MIRENA		✓	
Un-common	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	✓		
	Persistent lower abdominal pain, together with fever or unusual discharge from the vagina, possibly meaning pelvic infection.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN, AND WHAT TO DO ABOUT THEM				
Symptom / possible side effect		**Talk with your healthcare professional or pharmacist**		**Get immediate medical help**
		Only if severe	**In all cases**	
	Persistent lower abdominal pain, together with nausea or breast tenderness and/or vaginal bleeding, possibly meaning intrauterine pregnancy, miscarriage, or ectopic pregnancy.		✓	
	Dizziness		✓	
Very Rare	Allergic reaction including itchiness, rash, swelling of face and lips, cheeks, tongue and/or throat			✓

See also the section of this leaflet titled The Risks of Using MIRENA, Circulatory Disorder.

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

HOW TO STORE IT

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

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.bayer.ca or by contacting the sponsor at the above mentioned phone number and email address.

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