MIRENA®

Physician Prescribing Information

Mirena®
levonorgestrel-releasing intrauterine system

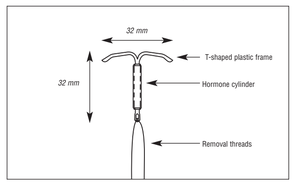
MIRENA®
(levonorgestrel-releasing intrauterine system)

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES

Rx only

DESCRIPTION

MIRENA® (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a barium sulfate, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body.

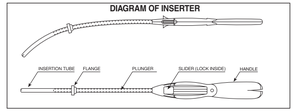


Schematic drawing of **MIRENA®**

INSERTER

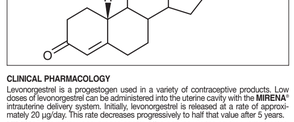
MIRENA® is packaged sterile within an inserter. The inserter, which is used for insertion of **MIRENA®** into the uterine cavity, consists of a symmetric top-slider body and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. Once **MIRENA®** is in place, the inserter is discarded.

DIAGRAM OF INSERTER



MIRENA® is intended to provide an initial release rate of 20 µg/day of levonorgestrel.

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in **MIRENA®**, has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



CLINICAL PHARMACOLOGY

Levonorgestrel is a progestogen used in a variety of contraceptive products. Low doses of levonorgestrel can be administered into the uterine cavity with the **MIRENA®** intrauterine delivery system. Initially, levonorgestrel is released at a rate of approximately 20 µg/day. This rate decreases progressively to half that value after 5 years.

MIRENA® has mainly local progestogenic effects in the uterine cavity. Morphological changes of the endometrium are observed, including stromal pseudodecidualization, glandular atrophy, a leucocytic infiltration and a decrease in glandular and stromal mitoses.

Ovulation is inhibited in some women using **MIRENA®**. In a 1-year study approximately 45% of menstrual cycles were ovulatory and in another study after 4 years 75% of cycles were ovulatory.

The local mechanism by which continuously released levonorgestrel enhances contraceptive effectiveness of the IUS has not been conclusively demonstrated. Studies of **MIRENA®** prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.

Clinical Pharmacokinetics

Following insertion of **MIRENA®**, the initial release of levonorgestrel into the uterine cavity is 20 µg/day. A stable plasma level of levonorgestrel of 150-200 pg/mL occurs after the first few weeks following insertion of **MIRENA®**. Levonorgestrel levels after long term use of 12, 24, and 60 months were 160±66 pg/mL, 192±140 pg/mL, and 159±59 pg/mL, respectively. The plasma concentrations achieved by **MIRENA®** are lower than those seen with levonorgestrel contraceptive implants and with oral contraceptives. Unlike oral contraceptives, plasma levels with **MIRENA®** do not display peaks and troughs.

The mean ± SD levonorgestrel endometrial tissue concentration in four women using levonorgestrel intrauterine systems releasing 30 µg/day of levonorgestrel for 36-49 days was 808 ± 511 ng/g wet tissue weight. The endometrial tissue concentration in 2 women who had been taking a 250 µg levonorgestrel-containing oral contraceptive for 7 days was 3.5 ng/g wet tissue weight. In contrast, Fallopian tube and myometrial levonorgestrel tissue concentrations were of the same order of magnitude in the **MIRENA®** group and the oral contraceptive group (between 1 and 5 ng/g of wet weight of tissue).

The pharmacokinetics of levonorgestrel itself have been extensively studied and reported in the literature. Levonorgestrel in serum is primarily bound to proteins (mainly sex hormone binding globulin) and is extensively metabolized to a large number of inactive metabolites. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in levonorgestrel concentrations seen in individuals using levonorgestrel-containing contraceptive products. The elimination half-life of levonorgestrel after daily oral doses is approximately 17 hours; both the parent drug and its metabolites are primarily excreted in the urine.

Pharmacokinetic studies of this product have not been conducted in special populations (pediatric, renal insufficiency, hepatic insufficiency, and different ethnic groups).

Drug-Drug Interactions:

The effect of other drugs on the efficacy of **MIRENA®** has not been studied.

INDICATIONS AND USAGE

MIRENA® is indicated for intrauterine contraception for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced.

RECOMMENDED PATIENT PROFILE

MIRENA® is recommended for women who have had at least one child, are in a stable, mutually monogamous relationship, have no history of pelvic inflammatory disease, and have no history of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

Clinical Studies

MIRENA® has been studied for safety and efficacy in two large clinical trials in Finland and Sweden, in study sites having verifiable data and informed consent. 1169 women 18 to 35 years of age at enrollment used **MIRENA®** for up to 5 years, for a total of 45,000 women-months of exposure. The study population was predominantly Caucasian, and over 70% of the participants had previously used IUDs. The reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women. However, due to limitations of the available data a precise estimate of the pregnancy rate is not possible.

The following table provides estimates of the percent of women likely to become pregnant while using a particular contraceptive method in the year. These estimates are based on a variety of studies. In this table, **MIRENA®** is identified as "LNg 20".

Table 1: Percentage of women experiencing an unintended pregnancy during the first year of typical use and first year of perfect use of contraception and the percentage continuing use at the end of the first year. United States

	% of Women Experiencing an Accidental Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[4]
Method (1)	**Typical Use[1] (2)**	**Perfect Use[2] (3)**	**(4)**
Chance[3]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Sympto-thermal[6]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
progestin only		0.5	
combined		0.1	
IUD:			
Progesterone T:	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, *Contraceptive Technology: Seventeenth Revised Edition*. New York NY: Irvington Publishers, 1998.

1 Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

2 Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.

3 Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

4 The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

5 Foams, creams, gels vaginal suppositories, and vaginal film.

6 Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

7 With spermicidal cream or jelly.

8 Without spermicides.

CONTRAINDICATIONS

MIRENA® insertion is contraindicated when one or more of the following conditions exist:

1. Pregnancy or suspicion of pregnancy.
2. Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity.
3. Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy.
4. Postpartum endometritis or infected abortion in the past 3 months.
5. Known or suspected uterine or cervical neoplasia or unresolved, abnormal Pap smear.
6. Genital bleeding of unknown etiology.
7. Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled.
8. Acute liver disease or liver tumor (benign or malignant).
9. Woman or her partner has multiple sexual partners.
10. Conditions associated with increased susceptibility to infections with microorganisms. Such conditions include, but are not limited to, leukemia, acquired immune deficiency syndrome (AIDS), and I.V. drug abuse.
11. Genital actinomycosis (See WARNINGS)
12. A previously inserted IUD that has not been removed.
13. Hypersensitivity to any component of this product.
14. Known or suspected carcinoma of the breast.
15. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

WARNINGS:

1. Ectopic Pregnancy

In large clinical trials of **MIRENA®**, half of all pregnancies detected during the studies were ectopic. The per-year incidence of ectopic pregnancy in the clinical trials was approximately 1 ectopic pregnancy per 1000 users per year. The rate of ectopic pregnancies associated with **MIRENA®** use is not significantly different than the rate for sexually active women not using any contraception.

Clinical trials of **MIRENA®** excluded women with a history of ectopic pregnancy. **MIRENA®** is not recommended for use in women with a history of ectopic pregnancy or conditions that increase the risk of ectopic pregnancy. Women who choose **MIRENA®** must be warned about the risks of ectopic pregnancy. They should be taught to recognize and report to their physician promptly any symptoms of ectopic pregnancy. Women should also be informed that ectopic pregnancy has been associated with complications leading to loss of fertility.

2. Intrauterine Pregnancy

In the event of an intrauterine pregnancy with **MIRENA®**, the following should be considered.

a. Septic abortion

In patients becoming pregnant with an IUD in place, septic abortion – with septicemia, septic shock, and death – may occur. If pregnancy should occur with a **MIRENA®** in place, **MIRENA®** should be removed. Removal or manipulation of **MIRENA®** may result in pregnancy loss.

b. Continuation of pregnancy

If a woman becomes pregnant with **MIRENA®** in place and 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. She should be followed closely and advised to report immediately any flu-like symptoms, fever, chills, cramping, 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. Because the information administration of levonorgestrel and local exposure to the hormone, the possibility of teratogenicity following exposure to **MIRENA®** cannot be completely excluded. Clinical experience with the outcomes of pregnancies is limited due to the small number of reported pregnancies following exposure to **MIRENA®**.

Congenital anomalies have occurred infrequently when **MIRENA®** has been in place during pregnancy. In these cases the role of **MIRENA®** in the development of the congenital anomalies is unknown. As of September 1999, 32 live births following exposure to **MIRENA®** were reported retrospectively. All but 2 of the infants were healthy at birth. One infant had pulmonary artery hypoplasia and another infant had cystic hypoplastic kidneys. (A sibling of this infant had renal agenesis with no **MIRENA®** exposure.)

3. Sepsis

As of 1999, four cases of Group A streptococcal sepsis (GAS) out of an estimated 1.3 million **MIRENA®** users were reported. All four women experienced the symptom of severe pain within hours of insertion, and this was followed by sepsis within a few days (of insertion). All recovered with treatment. Since death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during **MIRENA®** insertion is essential. (GAS sepsis can also occur postpartum, after minor surgery, in wounds and in association with other IUDs.)

4. Pelvic Inflammatory Disease (PID)

MIRENA® is contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy. Use of IUDs has been associated with an increased risk of PID. The highest risk of PID occurs shortly after insertion (usually within the first 20 days thereafter) (see **Insertion Precautions**). A decision to use **MIRENA®** must include consideration of the risks of PID.

a. Women at increased risk for PID

PID is often associated with a sexually transmitted disease, and **MIRENA®** does not protect against sexually transmitted disease. The risk of PID is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have ever had PID are at increased risk for a recurrence or re-infection.

b. PID warning to **MIRENA®** users

All women who choose **MIRENA®** must be informed prior to insertion about the possibility of PID and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or in infrequent cases can necessitate hysterectomy, or can cause death. Patients must be taught to recognize and report to their physician promptly any symptoms of pelvic inflammatory disease. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever.

c. Asymptomatic PID

PID may be asymptomatic but still result in tubal damage and its sequelae.

d. Treatment of PID

Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly. Removal of **MIRENA®** after initiation of antibiotic therapy is usually appropriate. Guidelines for PID treatment are available from the Center for Disease Control (CDC), Atlanta,Georgia. Adequate PID treatment requires the application of current standards of therapy prevailing at the time of occurrence of the infection with reference to prescription labeling.

Actinomycosis has been associated with IUDs. Symptomatic women with IUDs should have the IUD removed and should receive antibiotics. However, the management of the asymptomatic carrier is controversial because actinomycetes can be found normally in the genital tract cultures in healthy women without IUDs. False positive findings of actinomycosis on Pap smears can be a problem. When possible, confirm the Pap smear diagnosis with cultures.

5. Irregular Bleeding and Amenorrhea

MIRENA® can alter the bleeding pattern. During the first three to six months of **MIRENA®** use the number of bleeding and spotting days may be increased and bleeding patterns may be irregular. Thereafter the number of bleeding and spotting days usually decreases but bleeding may remain irregular. If bleeding irregularities develop during prolonged treatment appropriate diagnostic measures should be taken to rule out endometrial pathology.

Amenorrhea develops in approximately 20% of **MIRENA®** users by one year. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are not necessary in amenorrheic subjects unless indicated by other signs of pregnancy or by pelvic pain.

6. Embedment

Partial penetration or embedment of **MIRENA®** in the myometrium may decrease contraceptive effectiveness and can result in difficult removal.

7. Perforation

An IUD may perforate the uterus or cervix, most often during insertion although the perforation may not be detected until some time later. If perforation occurs, the IUD must be removed and surgery may be required. Adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera have been reported with IUDs.

It is recommended that postpartum **MIRENA®** insertion be delayed until uterine involution is complete to decrease perforation risk. There is an increased risk of perforation in women who are lactating. 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.

8. Ovarian Cysts

Since the contraceptive effect of **MIRENA®** is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age using **MIRENA®**. Sometimes atresia of the follicle is delayed and the follicle may continue to grow. Enlarged follicles have been diagnosed in about 12% of the subjects using **MIRENA®**. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases the enlarged follicles disappear spontaneously during two to three months observation. Surgical intervention is not usually required.

9. Breast Cancer

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer is a hormone-sensitive tumor.

10. Risks of Mortality

The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death include the combined risk of the contraceptive method and the risk of pregnancy or abortion in the event of method failure. The findings of the analysis are shown in Table 2.

Table 2: Annual Number of Birth-Related or Method-Related Deaths Associated with Control of Fertility per 100,000 Nonsterile Women, by Fertility Control Method According to Age

	AGE GROUP					
METHODS	15–19	20–24	25–29	30–34	35–39	40–44
No Birth Control Method/Term	4.7	5.4	4.8	6.3	11.7	20.6
No Birth Control Method/AB	2.1	2.0	1.6	1.9	2.8	5.3
IUD	0.2	0.3	0.2	0.1	0.3	0.6
Periodic Abstinence	1.4	1.3	0.7	1.0	1.0	1.9
Withdrawal	0.9	1.7	0.9	1.3	0.8	1.5
Condom	0.6	1.2	0.6	0.9	0.5	1.0
Diaphragm/Cap	0.6	1.1	0.6	0.9	1.6	3.1
Sponge	0.8	1.5	0.8	1.1	2.2	4.1
Spermicides	1.6	1.9	1.4	1.9	1.5	2.7
Oral Contraceptives	0.8	1.3	1.1	1.8	1.0	1.9
Implants/Injectables	0.2	0.6	0.5	0.8	0.5	0.6
Tubal Sterilization	1.3	1.2	1.1	1.1	1.2	1.3
Vasectomy	0.1	0.1	0.1	0.1	0.1	0.2

Harlap S. et al., *Preventing Pregnancy, protecting health: a new look at birth control choices in the US. The Alan Guttmacher Institute 1991: 1-129*

PRECAUTIONS

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

1. PATIENT COUNSELING

Prior to insertion, the physician, nurse, or other trained health professional must provide the patient with the Patient Package Insert. The patient should be given the opportunity to read the information and discuss fully any questions she may have concerning **MIRENA®** as well as other methods of contraception.

Careful and objective counseling of the user prior to insertion regarding the expected bleeding pattern, the possible interindividual variation in changes in bleeding and the etiology of the changes may have an effect on the frequency of removal due to bleeding problems and amenorrhea.

The patient should be told that some bleeding such as irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her health care provider. She should also be given instructions on what other symptoms require her to call her health care provider. She should be instructed on how to check after her menstrual period to make certain that the thread still protrudes from the cervix and cautioned not to pull on the thread and displace **MIRENA®**. She should be informed that there is no contraceptive protection if **MIRENA®** is displaced or expelled.

EVALUATION AND CLINICAL CONSIDERATIONS

a. A complete medical and social history, including that of the partner, should be obtained to determine conditions that might influence the selection of an IUD for contraception (see **CONTRAINDICATIONS**). A physical examination should include a pelvic examination, a Pap smear, and appropriate tests for any other forms of genital disease, such as gonorrhea and chlamydia laboratory evaluations, if indicated. **Special attention must be given to ascertaining whether the woman is at increased risk of ectopic pregnancy or PID. MIRENA® is contraindicated in these women.**

b. **The health care provider should determine that the patient is not pregnant.** The possibility of insertion of **MIRENA®** in the presence of an existing undetermined pregnancy is reduced if insertion is performed within 7 days of the onset of a menstrual period. **MIRENA®** can be replaced by a new system at any time in the cycle. **MIRENA®** can be inserted immediately after first trimester abortion.

c. **MIRENA®** should not be inserted until 6 weeks postpartum or until involution of the uterus is complete in order to reduce the incidence of perforation and expulsion.

d. Patients with certain types of valvular or congenital heart disease and surgically constructed systemic-pulmonary shunts are at increased risk of infective endocarditis. Use of **MIRENA®** in these patients may represent a potential source of septic emboli. Patients with known congenital heart disease who may be at increased risk should be treated with appropriate antibiotics at the time of insertion and removal. Patients requiring chronic corticosteroid therapy or insulin for diabetes should be monitored with special care for infection.

e. **MIRENA®** should be used with caution in patients who have a coagulopathy or are receiving anticoagulants.

f. Use of **MIRENA®** in patients with vaginitis or cervicitis should be postponed until proper treatment has eradicated the infection and until it has been shown that the cervix is not due to gonorrhea or chlamydia (see **CONTRAINDICATIONS**).

2. Insertion Precautions

Because the presence of organisms capable of establishing PID cannot be determined by appearance, and because IUD insertion may be associated with introduction of vaginal bacteria into the uterus, strict asepsis should be observed at insertion. Administration of antibiotics may be considered, but the utility of this treatment is unknown.

The uterus should be carefully sounded prior to **MIRENA®** insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

Syncope, bradycardia, or other neurovascular episodes may occur during insertion or removal of **MIRENA®**, especially in patients with a predisposition to these conditions or cervical stenosis. If increased pallor, perspiration, or pallor are observed, the patient should remain supine until these signs have disappeared.

3. Continuation and Removal

MIRENA® must be replaced every 5 years because contraceptive effectiveness after 5 years has not been established.

a) User complaints of pain, odorous discharge, bleeding, fever, genital lesions or sores should be promptly responded to and prompt examination recommended. (See **WARNINGS** regarding amenorrhea).

b) If examination during visits subsequent to insertion reveals that the length of the threads has changed from the length at time of insertion, and the system is verified as displaced, it should be removed. A new system may be inserted at that time or during the next menses if it is certain that conception has not occurred. If the threads are not visible, location of the **MIRENA®** should be verified, for example with X-ray, ultrasound, or gentle probing of the uterine cavity. If the **MIRENA®** is in place with no evidence of perforation, no intervention is indicated. If expulsion has occurred, it may be replaced within 7 days of a menstrual period after pregnancy has been ruled out.

c) Since **MIRENA®** may be displaced, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within 3 months after insertion. Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of **MIRENA®**. As menstrual flow usually decreases after the first 3 to 6 months of **MIRENA®** use, increase of menstrual flow may be indicative of an expulsion.

d) In the event a pregnancy is confirmed during **MIRENA®** use, the following steps should be taken:

- Determine whether pregnancy is ectopic and take appropriate measures if it is.
- Inform patient of the risks of leaving **MIRENA®** in place or removing it during pregnancy and of the lack of data on long-term effects on the offspring of women who have had **MIRENA®** in place during conception or gestation (see **WARNINGS**).
- If possible **MIRENA®** should be removed after the patient has been warned of the risks of miscarriage. If removal is difficult, the patient should be counseled and offered pregnancy termination.
- If **MIRENA®** is left in place, the patient's course should be followed closely.

e) Should the patient's relationship cease to be mutually monogamous, or should her partner become HIV positive, or acquire a sexually transmitted disease, she should be instructed to report this change to her clinician immediately. The use of a barrier method as a partial protection against acquiring sexually transmitted diseases should be strongly recommended. Removal of **MIRENA®** should be considered.

f) **MIRENA®** should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia; acquired immune deficiency syndrome (AIDS); sexually transmitted disease; pelvic infection; endometritis; symptomatic genital actinomycosis; intractable pelvic pain; severe dyspareunia; pregnancy; endometrial or cervical malignancy; uterine or cervical perforation.

g) If the retrieval threads are not visible, they may have retracted into the uterus or have been broken, or **MIRENA®** may have been broken, perforated the uterus, or have been expelled. Location of **MIRENA®** may be determined by sonography, X-ray, or by gentle exploration of the uterine cavity with a probe.

h) Removal of the system should also be considered if any of the following conditions arise for the first time:

- migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia;
- exceptionally severe headache;
- jaundice;
- marked increase of blood pressure;
- severe arterial disease such as stroke or myocardial infarction.

4. Glucose Tolerance

Levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of **MIRENA®**.

DRUG INTERACTIONS

The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes. The influence of these drugs on the contraceptive efficacy of **MIRENA®** has not been studied.

CARCINOGENESIS

Long-term studies in animals to assess the carcinogenic potential of levonorgestrel releasing intrauterine system have not been performed. See "**WARNINGS**" section.

PREGNANCY

Pregnancy Category X. See "**WARNINGS**" section.

NURSING MOTHERS

Levonorgestrel has been identified in small quantities in the breast milk of lactating women using **MIRENA®**. In a study of 14 breastfeeding women using a **MIRENA®** prototype during lactation, mean infant serum levels of levonorgestrel were approximately 7% of maternal serum levels. Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation.

PEDIATRIC USE

Safety and efficacy of **MIRENA®** have been established in women of reproductive age. Use of this product before menarche is not indicated. (See **RECOMMENDED PATIENT PROFILE**)

GERIATRIC USE

MIRENA® has not been studied in women over age 65 and is not currently approved for use in this population.

INFORMATION FOR THE PATIENT See Patient Labeling

Patients should also be advised that the prescribing information is available to them at their request. It is recommended that potential users be fully informed about the risks and benefits associated with the use of **MIRENA®**, with other forms of contraception, and with no contraception at all.

Return to fertility

About 80% of women wishing to become pregnant conceived within 12 months after removal of **MIRENA®**.

ADVERSE REACTIONS

The most serious adverse reactions associated with the use of **MIRENA®** are discussed above in the Warnings section. Others are presented in the Precautions section. Other adverse events reported by 5% or more subjects include:

Abdominal pain	Upper respiratory infection
Leukorrhea	Nausea
Headache	Nervousness
Vaginitis	Dysmenorrhea
Back pain	Weight increase
Breast pain	Skin disorder
Acne	Decreased libido
Depression	Abnormal Pap smear
Hypertension	Sinusitis

Other reported adverse reactions occurring in less than 3% of patients include: failed insertion, migraine, vomiting, anemia, cervicitis, dyspareunia, hair loss, eczema.

HOW SUPPLIED

MIRENA® (levonorgestrel-releasing intrauterine system), containing a total of 52 mg levonorgestrel, is available in a carton of one sterile unit NDC# 50419-421-01. Each **MIRENA®** is packaged in a thermoformed blister package with a peelable lid, together with an insertion tube.

MIRENA® is supplied sterile. **MIRENA®** is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

STORAGE AND HANDLING

Store at 25°C (77°F); with excursions permitted between 15°-30°C (59-86°F) [See USP Controlled Room Temperature]

DIRECTIONS FOR USE

NOTE: Health care providers are advised to become thoroughly familiar with the insertion instructions before attempting insertion of MIRENA®.

Insertion Instructions

MIRENA® is inserted with the provided inserter (figure 1) into the uterine cavity within seven days of the onset of menstruation or immediately after first trimester abortion by carefully following the insertion instructions. It can be replaced by a new system at any time during the menstrual cycle.

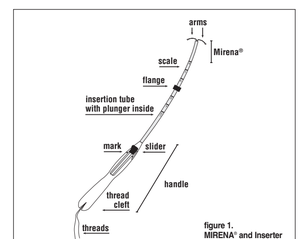


figure 1.
MIRENA® and Inserter

Preparation for insertion

- Confirm that the patient understands the method and alternatives and has signed a consent form.
- Examine the patient to establish the size and position of the uterus, to detect cervicitis or other genital contraindications and to exclude pregnancy.
- Obtain cervical cultures, perform a pregnancy test and give antibiotic prophylaxis if indicated.
- Use aseptic technique during insertion.
- Administer oral analgesics if needed.
- Cleanse the cervix and vagina with an antiseptic solution.
- Administer a paracervical block if needed.
- Grasp the upper lip of the cervix with a tenaculum and apply gentle traction to align the cervical canal with the uterine cavity.
- Carefully sound the uterus to measure its depth and to check the patency of the cervix. If you encounter cervical stenosis, use dilatation, not force, to overcome resistance.
- The uterus should sound to a depth of 6 to 9 cm. Insertion of **MIRENA®** into a uterine cavity less than 6.0 cm by sounding may increase the incidence of expulsion, bleeding, pain, perforation, and possibly, pregnancy.

Insertion Procedure

1.

- Open the sterile package.
- Place sterile gloves on your hands.
- Pick up the inserter containing **MIRENA®**.
- Carefully release the threads from behind the slider, so that they hang freely.
- Make sure that the slider is in the furthest position away from you (positioned at the top of the handle nearest the IUS).
- While looking at the insertion tube, check that the arms of the system are horizontal. If not, align them on a sterile surface (figure 2) or with sterile gloved fingers.

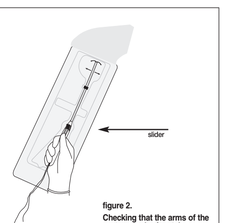


figure 2.
Checking that the arms of the system are horizontal

2.

- Pull on both threads to draw the **MIRENA®** system into the insertion tube (figure 3a).
- Note that the knobs at the ends of the arms now cover the open end of the inserter (figure 3b).

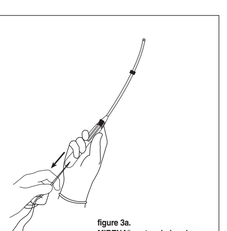


figure 3a.
MIRENA® system being drawn into the insertion tube

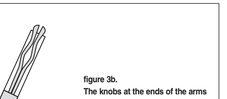


figure 3b.
The knobs at the ends of the arms

Physician Information

3. Fix the threads tightly in the cleft at the end of the handle (figure 4).

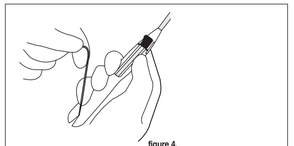


figure 4.
Threads are fixed tightly in the cleft

4. Set the flange to the depth measured by the sound, as indicated in figure 5.

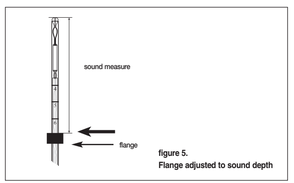


figure 5.
Flange adjusted to sound depth

5. MIRENA® is now ready to be inserted.
Hold the slider firmly in the furthermost position (at the top of the handle). Grasp the cervix with the tenaculum and apply gentle traction to align the cervical canal with the uterine cavity. Gently insert the inserter into the cervical canal and advance the insertion tube into the uterus until the flange is situated at a distance of about 1.5-2 cm from the external cervical os to give sufficient space for the arms to open (figure 6).
NOTE! Do not force the inserter.

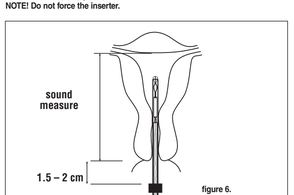


figure 6.
Inserting MIRENA®

6. While holding the inserter steady release the arms of **MIRENA®** (figure 7a) by pulling the slider back until the top of the slider reaches the mark (raised horizontal line on the handle) (figure 7b).

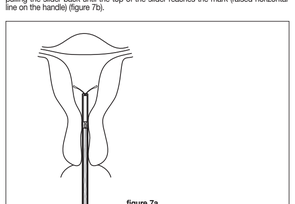


figure 7a.
The arms of the MIRENA® being released

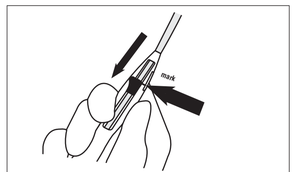


figure 7b.
Pulling the slider back to reach the mark

7. Push the inserter gently into the uterine cavity until the flange touches the cervix. **MIRENA®** should now be in the fundal position (figure 8).

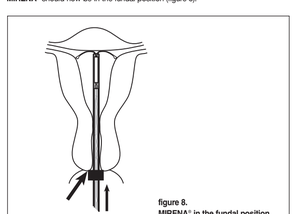


figure 8.
MIRENA® in the fundal position

8. Holding the inserter firmly in position release **MIRENA®** by pulling the slider down all the way. The threads will be released automatically (figure 9).

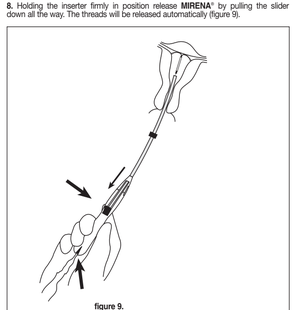


figure 9.
Releasing MIRENA® and withdrawing the inserter

9. Remove the inserter from the uterus. Cut the threads to leave about 2-3 cm visible outside the cervix (figure 10).

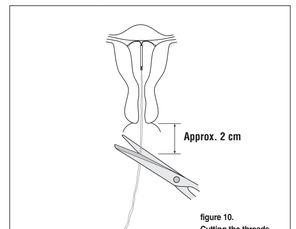


figure 10.
Cutting the threads

IMPORTANT!
If you suspect that the system is not in the correct position, check placement, (with ultrasound, for example). Remove the system if it is not positioned completely within the uterus. Do not reinsert a removed system.

REMOVAL OF MIRENA®
Remove **MIRENA®** by applying gentle traction on the threads with forceps. The arms of the system will fold upward as it is withdrawn from the uterus. The system should not remain in the uterus after 5 years.

SPECIAL NOTES IF A PATIENT WANTS TO CONTINUE CONTRACEPTION AFTER REMOVAL
You may insert a new **MIRENA®** immediately following removal.
If a patient with regular cycles wants to start a different birth control method, remove the system during the first 7 days of the menstrual cycle and start the new method.
If a patient with irregular cycles or amenorrhea wants to start a different birth control method, or if you remove the system after the seventh day of the menstrual cycle, start the new method at least 7 days before removal.

PATIENT INFORMATION

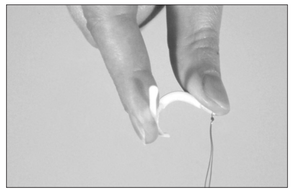
MIRENA®
(levonorgestrel-releasing intrauterine system)

MIRENA® (Mur-à-nah) is used to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

Read this information carefully before you decide if **MIRENA®** is right for you. This information does not take the place of talking with your health care provider. If you have any questions about **MIRENA®**, ask your health care provider. You should also learn about other birth control methods to choose the one that is best for you.

WHAT IS MIRENA®?
MIRENA® is a hormone-releasing system placed in your uterus to prevent pregnancy for up to 5 years.
MIRENA® is T-shaped. It contains a hormone called levonorgestrel. Levonorgestrel is a progestin hormone often used in birth control pills. **MIRENA®** releases the hormone into the uterus. Only small amounts of the hormone enter your blood.
Two brown threads are attached to the stem of the T. You can check that **MIRENA®** is in place by feeling for the threads at the top of your vagina with your fingers. Your health care provider can also remove **MIRENA®** at any time by pulling on the threads. The threads are the only part of **MIRENA®** you can feel when **MIRENA®** is in your uterus.

The **MIRENA®** is small...

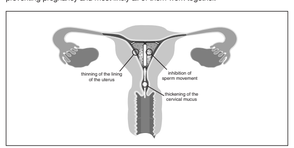


and flexible

What if I need birth control for more than 5 years?
You must have **MIRENA®** removed after 5 years, but your health care provider can insert a new **MIRENA®** then if you choose to continue using **MIRENA®**.

What if I change my mind about birth control and decide to have another baby?
Your health care provider can remove **MIRENA®** at any time by pulling on the threads. You may become pregnant as soon as **MIRENA®** is removed. About 8 out of 10 women who want to become pregnant will become pregnant some time in the first year after **MIRENA®** is removed.

How does MIRENA® work?
There is no single explanation of how **MIRENA®** works. It may stop release of your egg from your ovary, but this is not the way it works in most cases. It may block sperm from reaching or fertilizing your egg. It may make the lining of your uterus thin. We do not know which of these actions is most important for preventing pregnancy and most likely all of them work together.



How well does MIRENA® work?
Less than 1 out of 100 women using **MIRENA®** become pregnant during five years of **MIRENA®** use.
The following table shows how **MIRENA®** compares to other birth control methods. In this table **MIRENA®** is identified as "LNG 20".

Pregnancy Rates for Birth Control Methods
(For One Year of Use)

The following table provides estimates of the percent of women likely to become pregnant while using a particular contraceptive method for one year. These estimates are based on a variety of studies.

"Typical Use" *rates mean that the method either was not always used correctly or was not used with every act of sexual intercourse* (e.g., sometimes forgot to take a birth control pill as directed and became pregnant) *or was used correctly but failed anyway.*

"Lowest Expected" *rates mean that the method was always used correctly with every act of sexual intercourse but failed anyway* (e.g., always took a birth control pill as directed but still became pregnant).

Method	*Typical Use Rate of Pregnancy*	*Lowest Expected Rate of Pregnancy*
Sterilization		
Male Sterilization	0.15%	0.1%
Female Sterilization	0.5%	0.5%
Hormonal Methods:		
Implant (Norplant™ and Norplant-2™)	0.05%	0.05%
Hormone Shot (Depo-Provera)	0.3%	0.3%
Combined Pill (Estrogen/Progestin)	5%	0.1%
Minipill (Progestin only)	5%	0.5%
Intrauterine Devices (IUDs):		
Copper T	0.8%	0.6%
Progesterone T	2%	1.5%
LNG 20	0.1%	0.1%
Barrier Methods:		
Male Latex Condom [1]	14%	3%
Diaphragm [2]	20%	6%
Vaginal Sponge *(no previous births)* [3]	20%	9%
Vaginal Sponge *(previous births)* [3]	40%	20%
Cervical Cap *(no previous births)* [2]	20%	9%
Cervical Cap *(previous births)* [2]	40%	26%
Female Condom	21%	5%
Spermicide: *(gel, foam, suppository, film)*	26%	6%
Natural Methods:		
Withdrawal	19%	4%
Natural Family Planning *(calendar, temperature, cervical mucus)*	25%	1-9%
No Method:	85%	85%

1 Used Without Spermicide
2 Used With Spermicide
3 Contains Spermicide

Data adapted from: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, et al. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Ardent Media, 1998.

Who might use MIRENA®?
You might choose **MIRENA®** if you
- need birth control with a low failure rate
- need birth control that is reversible
- need birth control that is easy to use
- have had at least one baby

Who should not use MIRENA®?
Do not use **MIRENA®** if you
- might be pregnant
- have had a serious pelvic infection called pelvic inflammatory disease (PID)
- have had a serious pelvic infection in the past 3 months after a pregnancy
- have more than one sexual partner or your partner has more than one partner
- have an untreated pelvic infection now
- can get infections easily. For example, you have problems with your immune system, leukemia, AIDS, or intravenous drug abuse.
- might have cancer of the uterus or cervix
- have bleeding from the vagina that has not been explained
- have liver disease or liver tumor
- have breast cancer now or in the past
- have had an ectopic pregnancy or know you are at high risk for ectopic pregnancy
- have an intrauterine device in your uterus already
- have a condition of the uterus that distorts the uterine cavity, such as large fibroid tumors
- are allergic to levonorgestrel, silicone, or polyethylene

Tell your health care provider if you
- recently had a baby or if you are breast feeding
- are diabetic
- were born with heart disease or have problems with your heart valves
- have problems with blood clotting or take medicine to reduce clotting

How is MIRENA® inserted?
First, your health care provider will examine your pelvis to find the exact position of your uterus. Your health care provider will then clean your vagina and cervix with an antiseptic solution, and slide a thin plastic tube containing **MIRENA®** into your uterus. Your health care provider will then remove the plastic tube, leaving **MIRENA®** in your uterus. Finally, the strings will be cut to the proper length. Insertion takes only a few minutes.

How can I check that MIRENA® is in place?
You can check yourself by reaching up to the top of your vagina with clean fingers to feel the threads. Do not pull on the threads. It is a good habit to check **MIRENA®** after each menstrual period. If you feel more of **MIRENA®** than just the threads, **MIRENA®** is not in the right place. Call your health care provider to have it removed. If you cannot feel the threads at all, ask your health care provider to check that **MIRENA®** is still in the right place.
Return to your health care provider in the first 3 months after **MIRENA®** is inserted to make sure that **MIRENA®** is in the right place.
Using tampons will not change the position of **MIRENA®**.

What if I become pregnant while using MIRENA®?
Call your health care provider right away if you think you are pregnant. If you get pregnant while using **MIRENA®**, you may have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or abdominal pain may be a sign of ectopic pregnancy.
Ectopic pregnancy is an emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death. Do not use **MIRENA®** if you have had an ectopic pregnancy in the past or you are at high risk for ectopic pregnancy.
There are also risks if you get pregnant while using **MIRENA®** and the pregnancy is in the uterus. Severe infection, miscarriage, premature delivery, and even death can occur with pregnancies that continue with an intrauterine device. Because of this, your health care provider may try to remove **MIRENA®**, even though removing it may cause a miscarriage. If **MIRENA®** cannot be removed, talk with your health care provider about the benefits and risks of continuing the pregnancy.
If you continue your pregnancy, see your health care provider regularly. Call your health care provider right away if you get flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge, or fluid leaking from your vagina. These may be signs of infection.
We do not know if **MIRENA®** can cause long-term effects on the fetus if it stays in place during a pregnancy.

How will MIRENA® change my periods?
For the first 3 to 6 months, your monthly period may become irregular. You may also have frequent spotting or light bleeding. A few women have heavy bleeding during this time. After your body adjusts, the number of bleeding days is likely to decrease, and you may even find that your periods stop altogether.

What are the possible side effects of using MIRENA®?
The following are serious but uncommon side effects of **MIRENA®**
- Pelvic inflammatory disease (PID). Some IUD users get a serious pelvic infection called pelvic inflammatory disease. PID is usually sexually transmitted. You have a higher chance of getting PID if you or your partner have sex with other partners. PID can cause serious problems such as infertility, ectopic pregnancy or constant pelvic pain.
- PID is usually treated with antibiotics. However, more serious cases of PID may require surgery. A hysterectomy (removal of the uterus) is sometimes needed. In rare cases, infections that start as PID can even cause death.
  Tell your health care provider 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.
- Life-threatening infection. Life-threatening infection occurs rarely within the first few days after **MIRENA®** is inserted.Call your health care provider if you develop severe pain within a few hours after insertion.
- Perforation. **MIRENA®** may go through the uterus. This is called perforation. If your uterus is perforated, you may need surgery to remove **MIRENA®**. Perforation can cause internal scarring, infection, or damage to other organs.
- Expulsion. **MIRENA®** may come out by itself. This is called expulsion. You may become pregnant if **MIRENA®** comes out. Use a backup birth control method like condoms and call your health care provider if you notice that **MIRENA®** has come out.

There are several more common side effects of **MIRENA®**
- Cramps, dizziness, or faintness while **MIRENA®** is being inserted. This is common. Sometimes, the cramping is severe.
- Missed menstrual periods. About 2 out of 10 of women stop having periods after 1 year of **MIRENA®** use. The periods come back when **MIRENA®** is removed. If you do not have a period for 6 weeks during **MIRENA®** use, contact your health care provider.
- Changes in bleeding. You may have bleeding and spotting between menstrual periods, especially during the first 3 to 6 months. Sometimes the bleeding is heavier than usual at first. However, the bleeding usually becomes lighter than usual and may be irregular. Call your health care provider if the bleeding remains heavier than usual or if the bleeding becomes heavy after it has been light for a while.
- Cyst on the ovary. About 10% (1 out of 10) of women using **MIRENA®** will have a cyst on the ovary. These cysts usually disappear on their own in a month or two. However, cysts can cause pain and sometimes cysts will need surgery.

This is not a complete list of possible side effects. For more information, ask your health care provider.

When should I call my health care provider?
Call your health care provider if you have any concerns about **MIRENA®**. Be sure to call if you
- think you are pregnant
- have pelvic pain or pain during sex
- have unusual vaginal discharge or genital sores
- have unexplained fever
- might be exposed to sexually transmitted diseases (STDs)
- cannot feel **MIRENA®**'s threads
- develop very severe or migraine headaches
- have yellowing of the skin or whites of the eyes. These may be signs of liver problems.
- have a stroke or heart attack
- or your partner becomes HIV positive
- have severe or prolonged vaginal bleeding
- miss a menstrual period

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet summarizes the most important information about **MIRENA®**. If you would like more information, talk with your health care provider. You can ask your health care provider for information about **MIRENA®** that is written for health professionals.

2313005 (B) 6004703

Manufactured for:
Berlex
Montville, NJ 07045
Manufactured in Finland

This patient information booklet was written December 2000.

Fill out the following checklist. Your answers will help you and your health care provider decide if MIRENA® is a good choice for you.
Do you have any of these conditions?

	Yes	No	Don't know—will discuss with my health care provider
Abnormalities of the uterus	❑	❑	❑
Acquired immune deficiency syndrome (AIDS)	❑	❑	❑
Anemia or blood clotting problems	❑	❑	❑
Bleeding between periods	❑	❑	❑
Cancer of the uterus or cervix	❑	❑	❑
History of other types of cancer	❑	❑	❑
Steroid therapy (for example, prednisone)	❑	❑	❑
Possible pregnancy	❑	❑	❑
Diabetes	❑	❑	❑
Ectopic pregnancy in the past	❑	❑	❑
Fainting attacks	❑	❑	❑
Genital sores	❑	❑	❑
Heart disease	❑	❑	❑
Heart murmur	❑	❑	❑
Heavy menstrual flow	❑	❑	❑
Hepatitis or other liver disease	❑	❑	❑
Infection of the uterus or cervix	❑	❑	❑
IUD in place now or in the past	❑	❑	❑
IV drug abuse now or in the past	❑	❑	❑
Leukemia	❑	❑	❑
More than one sexual partner	❑	❑	❑
A sexual partner who has more than one sexual partner	❑	❑	❑
Pelvic infection	❑	❑	❑
Abortion or miscarriage in the past 2 months	❑	❑	❑
Pregnancy in the past 2 months	❑	❑	❑
Severe menstrual cramps	❑	❑	❑
Sexually transmitted disease (STD), such as gonorrhea or chlamydia	❑	❑	❑
Abnormal Pap smear	❑	❑	❑
Unexplained genital bleeding	❑	❑	❑
Uterine or pelvic surgery	❑	❑	❑
Vaginal discharge or infection	❑	❑	❑
HIV infection	❑	❑	❑
Breastfeeding	❑	❑	❑

Mirena®
(levonorgestrel-releasing intrauterine system)

Physician Information

Manufactured for:
BERLEX®
1-866-647-3646

Berlex, Montville, NJ 07045

Manufactured in Finland

2313005 (B) 6004703 September 2004