Data Sheet

MIRENA®

Levonorgestrel-releasing intrauterine delivery system (IUS)

Presentation

The product consists of an inserter and an intrauterine system (IUS) containing 52 mg levonorgestrel.

Uses

Actions

MIRENA is a small T-shaped intrauterine system (IUS) which after insertion releases the hormone levonorgestrel into the uterus. MIRENA contains a total amount of 52 mg levonorgestrel with an initial release rate of 20 microgram per 24 hours.

Levonorgestrel is a progestogen with anti-estrogenic activity used in gynaecology in a number of ways: as the progestogen component in oral contraceptives and in hormone replacement therapy, or alone for contraception in progestogen-only pills and subdermal implants. Levonorgestrel can also be administered into the uterine cavity as an intrauterine delivery system. This allows a very low daily dosage, as the hormone is released directly into the target organ.

Levonorgestrel is a potent progestin of the 19-nortestosterone class which possesses characteristic gestagenic properties such as endometrial transformation (development of a secretory endometrium), antigonadotropic action and antiestrogenic effects. The antiestrogenic activity of levonorgestrel is not the result of direct estrogen antagonism, since levonorgestrel does not bind to the estrogen receptor *in vitro*, but the result of modification of peripheral estrogenic effects. Levonorgestrel does not possess antiandrogenic or glucocorticoid properties, but does have marked partial androgenic activity.

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

The menstrual pattern is a result of the direct action of levonorgestrel on the endometrium and does not reflect the ovarian cycle. Bleeding patterns may vary from regular scanty menstruation in some women to oligo/amenorrhea in others. Amenorrhea is due to the local effect of levonorgestrel on the endometrium, which under strong local suppression does not proliferate in response to estrogen. In the process of inactivation

of endometrial proliferation, there can be an initial increase of spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in reduced duration and volume of menstrual bleeding. Scanty blood flow frequently develops into oligomenorrhea or amenorrhea.

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.

Clinical Studies

Contraception

The contraceptive efficacy of Mirena has been studied in 5 major clinical studies with 3330 women using Mirena. The failure rate (Pearl Index) was approximately 0.2 % at 1 year and the cumulative failure rate was approximately 0.7 % at 5 years. The failure rate also includes pregnancies due to undetected expulsions and perforations. Similar contraceptive efficacy has been observed in a large post-marketing study with more than 17000 women using Mirena. Because the use of Mirena does not require daily intake compliance by the users, the pregnancy rates in “typical use” are similar to those observed in controlled clinical trials (“perfect use”).The use of MIRENA does not alter the course of future fertility. About 80% of the women wishing to become pregnant conceived within 12 months after removal of the intrauterine system.

In clinical studies, during the first year of use 17% of women experienced amenorrhea of at least three months duration, but the cumulative gross discontinuation rate for amenorrhea was very low.

Menorrhagia

MIRENA can be successfully used in the treatment of idiopathic menorrhagia where no underlying pathology causing excessive bleeding can be found (see *Contraindications*). The volume of menstrual bleeding was decreased by 88% in menorrhagic women after three months of use. Another clinical trial (Study number 102-90528) compared the use of MIRENA with various standard oral treatments prior to a planned hysterectomy. More patients in the MIRENA group (67% compared to 15% in the reference group) decided to continue with MIRENA rather than proceed with hysterectomy).

Menorrhagia caused by submucosal fibroids may respond less favourably to treatment with MIRENA. Reduced bleeding increases the concentration of blood ferritin and hemoglobin. MIRENA also alleviates dysmenorrhea.

Hormone Replacement Therapy (HRT)

MIRENA provides the progestogenic component of continuous hormone replacement therapy (HRT). Due to the local administration, the systemic levonorgestrel concentration is very low.

To date, clinical data presented on the use of MIRENA for the prevention of endometrial hyperplasia has been from study trials of 24 months duration or less. Studies have demonstrated the efficacy of MIRENA in preventing endometrial hyperplasia during continuous estrogen treatment when administering estrogen either orally or transdermally. The observed hyperplasia rate under estrogen therapy alone is as high as 20% after one year of continuous treatment. In clinical studies with 201

perimenopausal and 259 postmenopausal users of MIRENA, no cases of endometrial hyperplasia were reported in the postmenopausal group during the observation period up to five years.

The concomitant estrogens used in the HRT studies were oral continuous estradiol valerate 2 mg/24 hours, continuous transdermal estradiol 50 microgram/24 hours, oral conjugated equine estrogen 0.625, 1.25 mg/day estradiol implants 36 microgram/24 hours and estradiol gel 1.5 mg/24 hours. MIRENA was effective in preventing endometrial hyperplasia in association with these regimens.

In clinical studies with MIRENA and copper IUDs used in contraception, no significant differences were found between the groups in serum levels of triglycerides, HDL cholesterol and total cholesterol after two and five years of treatment. The effect of MIRENA on lipid levels has been shown to be neutral,

Pharmacokinetics

Absorption

Following insertion Mirena releases levonorgestrel without delay. The high local drug exposure in the uterine cavity which is important for the local action of Mirena on the endometrium, leads to a strong concentration gradient via the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum>1000-fold). The in vivo release rate of levonorgestrel in the uterine cavity is initially approximately 20 microgram/24 hours and declines to 10 microgram/24 hours after 5 years.

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to SHBG. About 1-2 % of the circulating levonorgestrel is present as free steroid and 42-62 % is specifically bound to SHBG. During the use of Mirena, the concentration of SHBG declines. Accordingly, the fraction bound to SHBG decreases during the treatment and the free fraction increases. The mean apparent volume of distribution of levonorgestrel is about 106 L. After insertion of Mirena, levonorgestrel is detectable in serum after 1 hour. The maximum concentration is reached within 2 weeks after insertion. In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 picogram/mL (25^{th} to 75^{th} percentiles: 151 picogram/mL to 264 picogram/mL) at 6 months to 194 picogram/mL (146 mg/mL to 266 picogram/mL) at 12 months, and to 131 picogram/mL (113 picogram/mL to 161 picogram/mL) at 60 months in women of reproductive age weighing above 55 kg.

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

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

Metabolism

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

Elimination

The total clearance of levonorgestrel from plasma is approximately 1.0 mL/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted with the faeces and urine at an excretion ratio of about 1. The excretion half-life which is mainly represented by metabolites is about 1 day.

Indications

Contraception

Treatment of idiopathic menorrhagia provided there is no underlying pathology.

Prevention of endometrial hyperplasia during estrogen replacement therapy

Dosage and Administration

MIRENA is inserted into the uterine cavity. One administration is effective for five years.

The *in vivo* dissolution rate is approximately 20 microgram/24 hours initially and is reduced to 10 microgram/24 hours after five years. The mean dissolution rate of levonorgestrel is about 14 microgram /24 hours over the time up to five years

In women under hormone replacement therapy, MIRENA can be used in combination with oral or transdermal estrogen preparations without progestogens.

Mirena, when inserted according to the insertion instructions, has a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7 % at 5 years.

Insertion and Removal/Replacement

Before insertion, the woman must be informed of the efficacy, risks and side effects of MIRENA and the differences between the IUS and the copper intrauterine devices (IUDs). In particular, the woman should be informed about the expected differences in bleeding pattern, amenorrhea and hormonal effects. Studies have suggested that good counselling is likely to reduce unnecessary removals of MIRENA.

A physical examination, including pelvic and breast examinations, and a cervical smear should be performed. Pregnancy, sexually transmitted diseases and endometrial pathology should be excluded, and genital infections have to be successfully treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of MIRENA is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximise efficacy. Therefore, the instructions for insertion should be followed carefully. Because the insertion technique is different from other intrauterine devices, special emphasis

should be given to training in the correct insertion technique. The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

In women of reproductive potential, MIRENA is to be inserted into the uterine cavity within seven days of the onset of menstruation. MIRENA can be replaced by a new intrauterine system at any time in the cycle. The intrauterine system can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation.

When required for perimenopausal contraception and endometrial protection during short-term estrogen replacement therapy, MIRENA can be inserted during the last days of menstruation or withdrawal bleeding, or at any time in an amenorrheic woman.

Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of MIRENA. If the woman continues the use of MIRENA inserted earlier for contraception, endometrial pathology has to be excluded in the case of bleeding disturbances that appear after commencing estrogen replacement therapy. If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken.

Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient.

MIRENA is supplied in a sterile pack which should not be opened until required for insertion and only by a physician/health care professional experienced in the insertion of MIRENA. MIRENA should only be inserted if atropine and oxygen are available and it must always be inserted under aseptic conditions. If the seam of the sterile package is broken, the product should be discarded. Special instructions for insertion are in the package.

As the insertion technique for MIRENA is different from other intrauterine devices, special emphasis should be given to undergoing sufficient training in the correct insertion technique and the availability of appropriate instruments for the insertion of MIRENA.. It is recommended that Mirena should only be inserted by physicians/health care professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion

Following insertion, if it is suspected that the intrauterine system is not in the correct position, it should be removed and a new one inserted.

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

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

The intrauterine system should be removed after five years. If the user wishes to continue using the same method, a new intrauterine system can be inserted at the same time.

If pregnancy is not desired, the removal should be carried out during menstruation in women of reproductive potential, provided that there appears to be a menstrual cycle. If the intrauterine system is removed in mid-cycle and the woman has had intercourse within a week, she is at a risk of pregnancy unless a new intrauterine system is inserted immediately following removal.

Contraindications

Known or suspected pregnancy

Current or recurrent pelvic inflammatory disease

Lower genital tract infection

Postpartum endometritis

Infected abortion during the past three months

Cervicitis

Cervical dysplasia

Uterine or cervical malignancy

Progestogen-dependent tumors

Undiagnosed abnormal uterine bleeding

Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity

Conditions associated with increased susceptibility to infections

Acute liver disease or liver tumor

Hypersensitivity to the constituents of the preparation

Warnings and Precautions

MIRENA may be used with caution after specialist consultation, or removal of the intrauterine system should be considered, if any of the following conditions exist or arise for the first time:

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

MIRENA is not the method of first choice for nulligravid women.

Previous studies indicate that women with many sexual partners are more susceptible to infections (see "*Pelvic Infections"*).

MIRENA is not the method of choice for postmenopausal women with advanced uterine atrophy as the cervical canal is likely to be narrow, making insertion more difficult.

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

Heart Disease

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

Thrombosis

In women using progestogen-only pills, some epidemiological studies indicated a slightly increased risk of venous thromboembolism (VTE), but the results were statistically not significant. However, appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms or signs of thrombosis. Symptoms of venous or arterial thrombosis can 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 one part of the body; motor disturbances; "acute" abdomen. Symptoms or signs indicating retinal thrombosis are: unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Current evidence indicates that estrogen replacement therapy should only be used short-term and that in most circumstances, the risk of long-term estrogen replacement therapy outweighs the benefits (see NZ HRT guidelines). This needs to be taken into consideration when co-prescribing MIRENA for endometrial protection. In addition, where MIRENA is used for endometrial protection during estrogen replacement therapy, attention is drawn to all the data contained in the product information for estrogen-containing preparations. In particular all prospective and current users of estrogen-replacement preparations should be advised of the risks and benefits of treatment and the need for treatment should be reviewed frequently.

Diabetes

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of MIRENA. However, there is generally no need to alter the therapeutic regimen in diabetics using MIRENA.

Tumours

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of

the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Irregular bleeding/spotting is common during the first few months of therapy, however this may mask some symptoms and signs of endometrial polyps or cancer. Endometrial pathology should therefore be excluded before using MIRENA. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be taken.

Oligo/amenorrhea

In women of reproductive age, oligomenorrhea and/or amenorrhea develops gradually in about 20% of users. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. A repeated pregnancy test is not necessary in amenorrheic women unless indicated by other signs of pregnancy.

When MIRENA is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year. The rate of total amenorrhea for at least 90 days is about 30% when MIRENA is used in perimenopausal women, and 50% in postmenopausal women after 1 year. During prolonged use of MIRENA the amount of amenorrhea increases.

Pelvic infection

The insertion tube helps to protect MIRENA from contamination with micro-organisms during insertion and the MIRENA inserter has been designed to minimise the risk of infections. In users of copper intrauterine devices, the highest rate of pelvic infections occurs during the first month after insertion and decreases later. Some studies suggest that the rate of pelvic infection in users of MIRENA is lower than with copper-releasing intrauterine devices. A known risk factor for pelvic inflammatory disease is multiple sexual partners, especially in young and nulliparous women. Pelvic infection may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

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

Even when clinical symptoms indicate an infection, bacteriological examinations (to test for organisms such as chlamydia) are indicated and further gynecological monitoring over subsequent days is recommended in order to ensure proper diagnosis of the underlying infection.

Expulsion

Symptoms of the partial or complete expulsion of any IUS or IUD may include bleeding or pain. Other indications of partial expulsion include an increase in the length of the removal threads or if the stem of the intrauterine system is visible in the cervix. An ultrasonographic examination may be needed to ensure the proper fundal position of MIRENA. However, an intrauterine system can be expelled from the uterine cavity without the woman noticing it leading to a loss of contraceptive protection. Partial expulsion may decrease the effectiveness of MIRENA. As MIRENA decreases menstrual flow, increased menstrual flow may be indicative of an expulsion.

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

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

Perforation

Perforation or penetration of the uterine corpus or cervix by an intrauterine system may occur rarely, most often during insertion and may decrease the effectiveness of MIRENA. Excessive pain or bleeding during insertion may be indicative of a perforation. Should a perforation occur, the intrauterine system must be removed. The risk of perforations may be increased in post-partum insertions (see "*Dosage and Administration*"), in lactating women and in women with fixed retroverted uterus.

Ectopic pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain, especially in connection with missed periods or if an amenorrheic woman starts bleeding. The ectopic pregnancy rate with MIRENA is approximately 0.1% per year. This rate is lower than in women not using any contraception (0.3–0.5 % per year). The absolute risk of ectopic pregnancy in MIRENA users is low. However, when a woman becomes pregnant with MIRENA in situ, the relative likelihood of ectopic pregnancy is increased.

Sexually transmitted diseases

MIRENA does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs). The woman should be advised that additional measures, e.g. condoms, are needed to prevent the transmission of STDs.

Lost threads

If the retrieval threads are not visible at the cervix on follow-up examinations, pregnancy must be excluded. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, the intrauterine system may have been expelled. Ultrasound diagnosis may be used to ascertain the correct position of the intrauterine

system. If ultrasound is not available or successful, X-ray may be used to locate MIRENA.

Delayed follicular atresia

Since the contraceptive effect of MIRENA is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Enlarged follicles have been diagnosed in about 12% of women 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 within 2 - 3 months, but if they persist continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

Use in Pregnancy

Pregnancy Category B3. (Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

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

Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of virilizing effects in the fetus should be taken into consideration. . Clinical experience of the outcomes of pregnancies under MIRENA is limited due to its high contraceptive efficacy, but the woman should be informed that, to date, there is no evidence of birth defects caused by MIRENA use in cases where pregnancy continues to term with MIRENA in place.

Use in Lactation

About 0.1% of the maternal dose of levonorgestrel can be transferred via milk to the nursed infant, but it is unlikely that there will be a risk to the child with the low dose released from MIRENA.

There appears to be no adverse effect on infant growth or development when using MIRENA after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk.

Uterine bleeding has rarely been reported in women using MIRENA during lactation.

Effects on The Ability to Drive and Use Machinery

Not known

Preclinical Safety Data

Levonorgestrel is a well-established progestogen with anti-estrogenic activity. The safety profile following systemic administration is well documented. A study in monkeys with intrauterine delivery of levonorgestrel for 12 months confirmed local pharmacological activity with good local tolerance and no signs of systemic toxicity. No embryotoxicity was seen in the rabbit following intrauterine administration of levonorgestrel.

The preclinical safety evaluations revealed no specific hazard for humans based on studies of safety pharmacology, toxicity, genotoxicity and carcinogenic potential of levonorgestrel.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). Irregular bleeding patterns associated with the use of MIRENA could mask symptoms of cervical or endometrial cancer. Close clinical surveillance is essential in all women using MIRENA and in all cases of persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of malignancy. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing levonorgestrel. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal hemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

Saline, ethanol and DMSO extracts of MIRENA were without mutagenic activity when tested in histidine-dependent auxotrophs of *Salmonella typhimurium* and tryptophan-dependent auxotrophs of *Escherichia coli*. Saline and DMSO extracts of the medicine-releasing core of MIRENA were not mutagenic in mouse lymphoma cells or clastogenic in Chinese hamster ovary cells *in vitro* and they did not induce bone marrow micronuclei in mice *in vivo*. Saline and DMSO extracts of the polyethylene T-body of MIRENA were not mutagenic in bacteria or mouse lymphoma cells or clastogenic in human lymphocytes *in vitro* and neither saline or sesame oil extracts induced bone marrow nuclei in mice *in vivo*.

The safety evaluation of the elastomer components of the hormone reservoir, polyethylene materials of the product, and combination of elastomer and levonorgestrel, have not revealed bio-incompatibility. The evaluations were based on both the assessment of genetic toxicology in standard *in vitro* and *in vivo* test systems and on bio-compatibility tests in mice, guinea pigs, rabbits and *in vitro* test systems.

ADVERSE EFFECTS

Side effects are more common during the first months after insertion of MIRENA and subside during prolonged use.

Serious undesirable effects of MIRENA have been referred to in the "*Contraindications"* and "*Warnings and Precautions"* sections. In addition, the following undesirable effects have been reported:

Very common side effects (occurring in more than 10% of users) include uterine/vaginal bleeding (including spotting, oligomenorrhea and amenorrhea) and benign ovarian cysts.

In fertile women the average number of spotting days per month decreases gradually from nine to four days during the first six months of use.

The percentage of women with prolonged bleeding (more than eight days) decreases from 20% to 3% during the first three months of use. When used in combination with estrogen replacement therapy, most peri- and postmenopausal users of MIRENA experienced spotting and irregular bleeding during the first months of the treatment. Thereafter bleeding and spotting decreased and about 40% of the users became totally free of bleeding during the last three months of the first year of treatment. Bleeding disturbances were more frequent in perimenopausal women when compared with postmenopausal women.

The frequency of benign ovarian cysts depends on the diagnostic method used. In clinical trials, enlarged follicles (functional ovarian cysts) have been diagnosed in 12% of women using MIRENA. Most of the follicles are asymptomatic and disappear within three months.

The table below reports adverse reactions by system organ class. The frequencies are based on clinical trial data.

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10000 to < 1/1000)**
Psychiatric Disorders	Depressed mood Nervousness Decreased libido	Altered mood	
Nervous System Disorders	Headache	Migraine	
Gastrointestinal Disorders	Abdominal pain, nausea	Abdominal distension	
Skin and Subcutaneous Tissue Disorders	Acne	Alopecia Hirsuitism Pruritis Eczema	Rash Urticaria
Musculoskeletal, Connective Tissue and Bone Disorders	Back pain		
Reproductive	Pelvic pain,	Pelvic inflammatory	Uterine

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10000 to < 1/1000)
System and Breast Disorders	Dysmenorrhea vaginal discharge Vulvovaginitis Breast tenderness Beast pain Intra-uterine contraceptive device expulsion	disease Endometritis Cervicitis/Papanicolaou smear normal, class II	perforation
General Disorders and Administration Site Conditions		Edema	
Investigations	Weight gain		

When a woman becomes pregnant with MIRENA in situ, the relative risk of ectopic pregnancy is increased. In addition, cases of breast cancer have been reported in MIRENA users (frequency unknown, see "*Warnings and Precautions*").

Interactions

The metabolism of progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). The influence of these medicines on the contraceptive efficacy of MIRENA has not been studied, but it is not believed to be of major importance due to the mainly local mechanisms of action.

Overdosage

Not applicable

Pharmaceutical Precautions

Shelf life: 3 years

Special conditions for storage: Store the product below 25°C protected from direct sunlight and moisture.

Medicine Classification

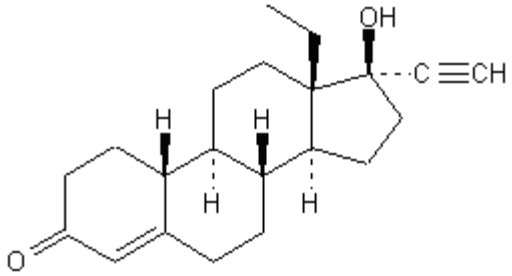
Prescription Medicine

Package Quantities

One levonorgestrel intrauterine system packed into a thermoformed blister package together with an inserter and sealed with a peelable lid.

Further Information

Levonorgestrel is a white or almost white, odorless or almost odorless, crystalline powder. It is insoluble in water or hexane, slightly soluble in ethanol or acetone, and sparingly soluble in methylene chloride. The chemical name for levonorgestrel is 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one. The CAS registry number for levonorgestrel is 797-63-7.



Chemical Formula: $C_{21}H_{28}O_2$

Molecular Weight: 312.45

Melting Point: 232-239 °C

The levonorgestrel (LNG) IUS consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The vertical stem of the levonorgestrel intrauterine system is loaded in the insertion tube at the tip of the inserter. Inserter components are an insertion tube, plunger, flange, body and slider. The intrauterine system consists of a white or almost white hormone-elastomer core, mounted on the vertical stem of a T-body and covered with an opaque tubing which regulates the release of levonorgestrel. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop. The intrauterine system is essentially free from visible impurities.

Nature and Contents of the Container

The product is single packed into a thermoformed blister package with a peelable lid.

Instructions for Use/Handling

MIRENA is supplied in a sterile pack which should not be opened until required for insertion by a professional experienced in the insertion of MIRENA. Because the insertion technique is different from other intrauterine devices, special emphasis should be given to training in the correct insertion technique. The exposed product should be handled with aseptic precautions. If the seam of the sterile package is broken, the IUS should be discarded as medicinal waste. A removed IUS and inserter should be handled as medicinal waste, since it may contain hormone remnants and blood

contaminants. For further information see "*Insertion and Removal/Replacement".* Special instructions for insertion are in the package.

List of Excipients

Polydimethylsiloxane elastomer, silica (colloidal anhydrous), polyethylene, barium sulfate, iron oxide Black C177499

Name and Address

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Hillcrest
North Shore
AUCKLAND 0627

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Date of Preparation

11 December 2009