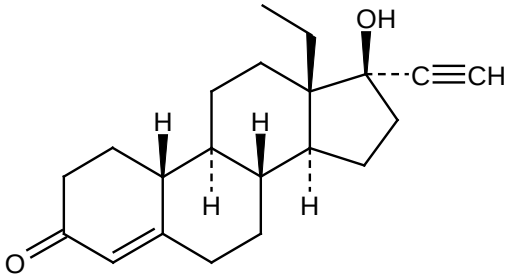
PRODUCT INFORMATION

MIRENA®

NAME OF THE MEDICINE

MIRENA 20 microgram per 24 hours intrauterine delivery system contains 52 mg levonorgestrel, a progestogen, as the active ingredient. MIRENA is also an intrauterine contraceptive device. The levonorgestrel initial release rate is 20 microgram per 24 hours.

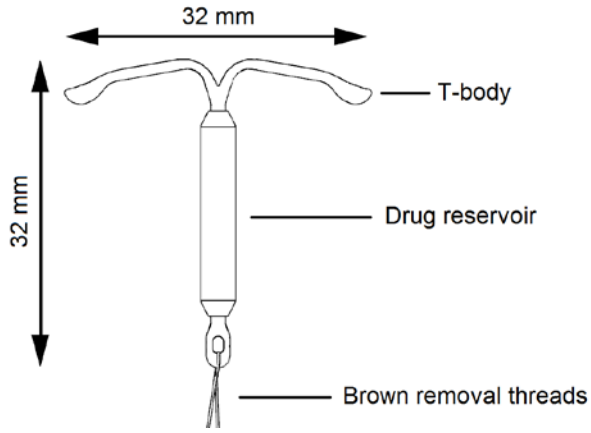
Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. It is insoluble in water or hexane, slightly soluble in ethanol or acetone, and sparingly soluble in methylene chloride. The chemical name for levonorgestrel is 13β-ethyl-17β-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one.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

DESCRIPTION

MIRENA is an intrauterine delivery system (IUS) based on a T-shaped polyethylene frame, with a cylinder containing a mixture of dimethylsiloxane/methylvinylsiloxane (cross-linked) elastomer and levonorgestrel around its vertical arm. The cylinder is covered by a dimethylsiloxane/methylvinylsiloxane (cross-linked) elastomer membrane, which regulates the release of levonorgestrel. It contains a total of 52 mg levonorgestrel. The levonorgestrel 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 white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Brown removal threads are attached to the loop. The T-body of MIRENA contains barium sulfate, which makes it visible in X-ray examination. The vertical stem of the IUS is loaded in the insertion tube at the tip of the inserter. The IUS and inserter are essentially free of visible impurities.



Excipients
Dimethylsiloxane/methylvinylsiloxane (cross-linked) elastomer, Silica - colloidal anhydrous, polyethylene, barium sulfate, iron oxide black CI77499.

PHARMACOLOGY

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.

Levonorgestrel is used in gynaecology as the progestogenic component in combined oral contraceptives and for contraception in progestogen-only pills. Levonorgestrel can also be administered into the uterine cavity with an intrauterine delivery system such as MIRENA. This allows a very low daily dosage, as the hormone is released directly into the uterine cavity.

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

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

Pharmacokinetics

Absorption
Following insertion, levonorgestrel is released from the IUS into the uterine cavity without delay based on serum concentration measurements.

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 (25th to 75th 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.

In postmenopausal women using MIRENA together with non-oral estrogen treatment, the median serum concentration of levonorgestrel declines from 257 picogram/mL (25th to 75th 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 estrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approximately 478 picogram/mL (25th to 75th percentiles: 341 picogram/mL to 655 picogram/mL) due to the induction of SHBG by oral estrogen treatment.

Distribution
Levonorgestrel is bound non-specifically to serum albumin and specifically to sex hormone–binding globulin (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.

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.

Metabolism
Levonorgestrel is extensively metabolised. 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.

CLINICAL TRIALS

Contraception
The contraceptive efficacy of MIRENA has been studied in 5 major clinical studies with 3330 women using MIRENA. Two of the 5 studies were 5-year studies and 3 were 1-year studies. The failure rate (Pearl Index) was 0.21% at 1 year (based on data from 3330 women) and 0.14% at 5 years (based on data from 2245 women). This Pearl Index also includes pregnancies due to undetected expulsions and perforations. The cumulative failure rate was 0.2% at 1 years and 0.71% at 5 years.

In a large, prospective, comparative, non-interventional cohort study with an observation period of one year including more than 43,000 MIRENA users, the Pearl Index of MIRENA was 0.06 (95% CI: 0.04-0.09).

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 following the removal of MIRENA.

Menstrual blood loss is generally reduced during use of MIRENA. Scanty blood flow frequently develops into oligomenorrhoea or amenorrhoea. Amenorrhoea is due to the local effect of levonorgestrel on the endometrium, which under strong local suppression, does not proliferate in response to estrogen. The menstrual pattern does not reflect the ovarian cycle. In the process of inactivation of the proliferation of the endometrium there can be an initial increase of spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in the reduction of the duration and volume of menstrual bleeding during use of MIRENA. The production of the ovarian hormones, progesterone and estradiol, remain within normal limits, even when the users of MIRENA are amenorrhoeic.

In clinical studies during the first year of use, 17% of women experienced amenorrhoea of at least three months' duration, but the cumulative gross discontinuation rate for amenorrhoea was very low. The most common adverse event with the use of MIRENA is the change in menstrual bleeding pattern. These changes may include spotting, shorter or longer menstrual periods, or oligo/amenorrhoea.

However spotting decreases gradually and the number of days spotting after six months was less than four, which was comparable to the experience with copper IUDs. During the first month of use, 20% of users experienced prolonged bleeding (more than eight days). For many women, periods became shorter and during the third month of use, only 3% of users had prolonged bleeding.

Although bleeding patterns may vary from regular scanty menstruation in some women to oligo/amenorrhoea in others, there is no clear difference in follicle development, ovulation or estradiol and progesterone production in women with different bleeding patterns.

Menorrhagia
MIRENA can be successfully used in the treatment of idiopathic menorrhagia, where no organic reasons for excessive bleeding can be found (see CONTRAINDICATIONS). Menorrhagia caused by submucosal fibroids may respond less favourably to treatment with MIRENA. Results from three comparative studies indicate that in menorrhagic women, menstrual blood loss decreased by 62-94% at the end of three months and by 71-95% at the end of six months of use. MIRENA appears to have similar effects to endometrial ablation/resection in reducing the menstrual blood loss up to two years. Reduced bleeding may increase ferritin and haemoglobin levels. MIRENA may also alleviate dysmenorrhoea.

The following table (see Table 1) indicates the effectiveness of MIRENA in the treatment of idiopathic menorrhagia from the clinical trials. The results indicate that menstrual blood loss was reduced by approximately 93% in women using MIRENA while the reduction in blood loss in the reference treatments was 63-100% depending upon the treatment. Another clinical trial (Study No. 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 with 15% in the reference group) decided to continue with MIRENA rather than proceed with the hysterectomy.

Table 1: Comparison between MIRENA (LNG IUS) and reference treatments on the extent of menstrual blood loss in women with idiopathic menorrhagia.

Study No.	Treatment (no. pts)	Duration of Study	Baseline values (range)	End of study values	Method of Analysis
102-94548	LNG IUS (28)	6 cycles	168 mL (80-348)	11 mL (0-151)	Objective[3]
	Tranexamic Acid (30)[5]		140 mL (81-569)	53 mL (21-528)	
102-92549	LNG IUS (22)	3 cycles	106 mL (82-780)	6 mL (0-284)	Objective[3]
	NET[1,6] (22)		120 mL (82-336)	21 mL (0-137)	
102-93503	LNG IUS (30)	12 months	268 (88-1498)	17 (0-463)	PBAC[4] score
	TCRE[2] (29)		271 (24-2519)	0 (0-61)	

[1]NET = Norethisterone, [2]TCRE = transcervical endometrial resection, [3]Objective = menstrual blood loss, [4]PBAC = pictorial blood loss assessment chart,
[5] Dosage: two 500mg tablets, 4 times a day for maximum 5 days during bleeding,
[6] Dosage: 15mg/day for 21 days in 28 day cycle.

Hormone Replacement Therapy (HRT)
MIRENA provides the progestogenic component of continuous HRT. Due to the local administration, the systemic levonorgestrel concentration is very low. The efficacy of MIRENA in preventing endometrial hyperplasia during continuous estrogen treatment has been equally efficacious 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 a total of 634 perimenopausal and postmenopausal users of MIRENA, no endometrial hyperplasias were reported during the observation period varying from one up to five years. To date, clinical data presented on the use of MIRENA for the prevention of endometrial hyperplasia has been in study trials of 24 months duration or less. 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.

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

INDICATIONS

MIRENA is indicated for:

- Contraception
- Treatment of idiopathic menorrhagia
- Prevention of endometrial hyperplasia during estrogen replacement therapy.

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
- confirmed or suspected hormone dependent tumours including breast cancer
- 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 tumour
- hypersensitivity to the active substance or to any of the excipients

PRECAUTIONS

General

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

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

MIRENA is not the method of first choice for young nulligravid women. Previous studies indicate that an increased number of sexual partners may increase susceptibility to sexually transmitted infections (see Pelvic Infections). MIRENA is not the first choice for postmenopausal women with advanced uterine atrophy as the cervical canal is likely to be narrow, making the insertion more difficult.

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.

Due to the limited exposure in MIRENA trials in the indication “prevention of endometrial hyperplasia during estrogen replacement therapy”, the available data is not sufficient to confirm or refute a risk for breast cancer when MIRENA is used in this indication. The product information of the estrogen replacement therapy should also be consulted for additional information.

Since a biological effect cannot be excluded, an individual benefit-risk assessment should be made in women in whom breast cancer is diagnosed while using MIRENA. Removal of MIRENA should be considered.

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

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.

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 Type 1 diabetics using MIRENA.

Oligo/amenorrhoea
In a study with women of fertile age using MIRENA, oligomenorrhoea and amenorrhoea developed gradually in about 57% and 16% of women, respectively, at the end of the first year of use. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of the previous menstruation. A repeated pregnancy test is not necessary in amenorrhoeic subjects 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 amenorrhoea 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 amenorrhoea increases.

Pelvic infection
The insertion tube helps to prevent MIRENA from contamination with microorganisms during the 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 the copper-releasing intrauterine devices. Known risk factors for pelvic inflammatory disease are multiple sexual partners. Pelvic infection may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynaecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUD insertion.

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 gynaecological monitoring over the subsequent days is recommended in order to ensure proper diagnosis of the underlying infection.

Expulsion
From the clinical studies with MIRENA, the 5-year gross cumulative expulsion rate was 2.2 to 5.8 per 100. Expulsion is reported as "common" or ≥ 1% and < 10% in the table which lists Adverse Drug Reactions. Symptoms of the partial or complete expulsion of any intrauterine device may include bleeding or pain. Other indications of a 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, the 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, increase of menstrual flow may be indicative of an expulsion.

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

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

Perforation
Perforation or penetration of the uterine corpus or cervix by an intrauterine device may occur, most often during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of MIRENA. Excessive pain or bleeding during insertion or while MIRENA is *in situ* may be indicative of a perforation. Such occurrences and/or lost threads should be further investigated. The frequency of perforations is similar to that with a copper intrauterine device (≥0.01% to <0.1%). Should a perforation occur, the system must be removed as soon as possible; surgery may be required.

In a large, prospective, comparative, non-interventional cohort study in IUD users (n=61,448 women), the incidence of perforation was 1.3 (95% CI: 1.1-1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1000 insertions in the MIRENA cohort and 1.1 (95% CI: 0.7-1.6) per 1000 insertions in the copper IUD cohort.

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

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

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion

Insertion ≤ 36 weeks after delivery	5.6 (95% CI: 3.9-7.9; n=6,047 insertions)	1.7 (95% CI: 0.8-3.1; n=5,927 insertions)
Insertion ≥ 36 weeks after delivery	1.6 (95% CI: 0-0.9.1; n=608 insertions)	0.7 (95% CI: 0.5-1.1; n=41,910 insertions)

The risk of perforations may be increased in women with fixed retroverted uterus.

Re-examination after insertion should follow the guidance given under the heading "Medical Examination" (see DOSAGE AND ADMINISTRATION), which may be adapted as clinically indicated in women with risk factors for perforation.

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 an ectopic pregnancy should be considered in the case of lower abdomen pain – especially in connection with missed periods or if an amenorrhoeic woman starts bleeding. In clinical trials, the ectopic pregnancy rate with MIRENA was approximately 0.1% per year. In a large, prospective, comparative, non-interventional cohort study with an observation period of one year, the ectopic pregnancy rate with MIRENA was 0.02%. 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 this pregnancy being ectopic is increased and urgent assessment is required (see ADVERSE EFFECTS).

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

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 appear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, the possibility of expulsion or perforation should be considered. Ultrasound diagnosis may be used to ascertain the correct position of the system. If ultrasound is not available or successful, X-ray may be used to locate MIRENA.

Ovarian Cysts
Since the contraceptive effect of MIRENA is mainly due to its local effect, ovulatory cycles with follicular rupture occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Ovarian cysts have been reported as adverse drug reactions in approximately 7% of women using MIRENA. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the ovarian cysts disappear spontaneously during two to three months observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

Carcinogenicity
No studies of the carcinogenic potential of MIRENA have been performed. 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 haemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

Genotoxicity
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 drug-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*.

Effects on Fertility
Studies have suggested that in women who discontinue MIRENA for planned pregnancy, the pregnancy rate at one year is similar to those who do not use contraception.

Use in Pregnancy: Category B3
MIRENA is not to be used during an existing or suspected pregnancy. If the woman becomes pregnant when using MIRENA, removal of the system is recommended, since any intrauterine contraceptive device 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. Ectopic pregnancy should be excluded. If the intrauterine contraceptive device cannot be gently removed, termination of the pregnancy may be considered. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be monitored closely. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of virilising effects in the fetus should be taken into consideration. Clinical experience of the outcomes of pregnancies under MIRENA is limited due to the 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.

When levonorgestrel-impregnated silastic devices were introduced into the uteri of pregnant rabbits, the incidence of late foetal resorption was increased when compared to sham-operated controls. There were no other effects on the foetuses that could be attributed specifically to the device or to levonorgestrel.

Use in Lactation
About 0.1% of the levonorgestrel dose is transferred to the infant during breastfeeding. However it is not likely that there will be a risk for the infant with the dose released from MIRENA when it is inserted in the uterine cavity. Uterine bleeding has rarely been reported in women using MIRENA during lactation. There appears to be no deleterious effects 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 (see 'Perforation' section under PRECAUTIONS).

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

Use in the Elderly
MIRENA has not been studied in women over the age of 65 years.

Patients with Hepatic Impairment
MIRENA is contraindicated in women with acute liver disease or liver tumour.

Patients with Renal Impairment
MIRENA has not been studied in women with renal impairment.

Effects on Ability to Drive or Use Machines
Not known

INTERACTIONS WITH OTHER MEDICINES

Interactions can occur with drugs that induce or inhibit microsomal enzymes, which can result in increased or decreased clearance of sex hormones.

Substances increasing the clearance of levonorgestrel, e.g.:
Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, rifabutin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort.

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

Substances with variable effects on the clearance of levonorgestrel:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestogen.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors), e.g.:
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

ADVERSE EFFECTS

Adverse events are more common during the first months after the insertion, and subside during prolonged use. In addition to the adverse effects listed in PRECAUTIONS, the following undesirable effects have been reported in users of MIRENA.

Menstrual problems are the most often reported adverse events as described below. The most common adverse effect of MIRENA is a change in menstrual bleeding patterns. The changes may include spotting, shorter or longer menstrual periods, irregular bleeding, oligomenorrhoea, amenorrhoea, heavy flow, back pain and period pain/dysmenorrhoea (see CLINICAL STUDIES).

The majority of women experience changes in menstrual bleeding pattern after insertion of MIRENA. In a study with women of fertile age using MIRENA, prolonged bleeding was experienced by 22% and irregular bleeding by 67% of women during the first 90 days after postmenstrual insertion of MIRENA, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, amenorrhoea is experienced by 0% and infrequent bleeding by 11% during the first 90 days, increasing to 16% and 57% at the end of the first year of use, respectively.

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 table below reports adverse reactions by MedDRA system organ classes with the frequencies based on clinical trial data. Frequencies are defined as:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)

The frequencies are crude incidences of the events observed in clinical trials for the indications “contraception” and “idiopathic menorrhagia” (with 5,091 women and 12,101 woman-years).

Adverse reactions in clinical trials in the indication “prevention of endometrial hyperplasia during estrogen replacement therapy” (with 514 women and 1,218.9 woman-years) were observed at a similar frequency unless specified by footnotes.

Table 3: Adverse reactions reported in clinical trials

System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**
Psychiatric disorders		Depressed mood/ Depression Nervousness Decreased libido	Altered mood	
Nervous system disorders	Headache	Migraine		
Gastrointestinal disorders	Abdominal /pelvic pain	Nausea	Abdominal distension	
Skin and subcutaneous disorders		Acne Hirsutism	Alopecia Pruritis Eczema	Rash Urticaria

System Organ Class	Very common	Common	Uncommon	Rare
Musculoskeletal, connective tissue and bone disorders		Back pain**		
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst Dysmenorrhoea Breast tenderness Breast pain** Intra-uterine contraceptive device expelled (complete and partial)	Cervicitis/Papanicolaou smear normal, class II	Uterine perforation***
General disorders and administration site conditions			Oedema	
Investigations		Weight increased		

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related condition.

* Endometrial prevention trials: "common"

** Endometrial prevention trials: "very common"

*** This frequency is based on clinical trials that excluded breastfeeding women. In a large, prospective, comparative, non-interventional cohort study in IUD users, the frequency of perforation in women who were breastfeeding or had an insertion up to 36 weeks after delivery was "uncommon" (see PRECAUTIONS).

Description of Post Market Adverse Reactions

Pregnancy, puerperium and perinatal conditions:

When a woman becomes pregnant with MIRENA *in situ*, the relative risk of ectopic pregnancy is increased. The ectopic pregnancy rate with MIRENA is approximately 0.1% per year (see Precautions).

Reproductive system and breast disorders

The system or parts of it may perforate the uterine wall (see PRECAUTIONS).

Functional ovarian cysts may develop, and have been diagnosed in about 7% of women using MIRENA. Most of these cysts are asymptomatic (see PRECAUTIONS).

Breast Disorders

Cases of breast cancer have been reported (frequency unknown), (see PRECAUTIONS). The risk of breast cancer is unknown when MIRENA is used in the indication "prevention of endometrial hyperplasia during estrogen replacement therapy".

Immune System Disorders:

Hypersensitivity including rash, urticaria and angioedema

Reproductive system disorders:
The removal threads may be felt by the partner during intercourse.

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

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

Investigations:
Blood pressure increased

DOSAGE AND ADMINISTRATION

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

Special instructions for insertion are in the package. The insertion technique differs to that for other intrauterine devices. Care must therefore be given to adequate training in the correct insertion technique and the availability of appropriate instruments for the insertion of MIRENA.

Medical Examination
Before insertion, the woman must be informed of the efficacy, risks and side effects of MIRENA. A physical examination including pelvic examination, examination of the breasts, and a cervical smear should be performed. Standard testing procedures should be used to exclude pregnancy and sexually transmitted diseases, and genital infections must have been 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. 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. The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Insertion and Removal of MIRENA
In women of fertile age, MIRENA is to be inserted into the uterine cavity within seven days of the onset of menstruation. MIRENA can be replaced by a new system at any time in the cycle. The system can also be inserted immediately after first trimester abortion. Postpartum 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 insertion, physical examination and ultrasound should be performed immediately to exclude perforation. MIRENA is not suitable for use as a post-coital contraceptive.

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

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.

Because irregular bleeding/spotting is common during the first months of therapy, endometrial pathology should be excluded 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 prolonged treatment, appropriate diagnostic measures should also be taken.

MIRENA is removed by gently pulling on the threads with forceps. If the threads are not visible and the system is in the uterine cavity, it may be removed using either ovum forceps or an IUD hook. This may require dilatation of the cervical canal or other surgical intervention.

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

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

After removal of MIRENA, the system should be checked to see if it is intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms hiding them inside the cylinder. Further intervention is not required 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.

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

OVERDOSAGE

Not applicable for this product.

PRESENTATION AND STORAGE CONDITIONS

MIRENA is supplied in a sterile pack, which should not be opened until required for insertion by a professional experienced in the insertion of intrauterine systems. The exposed product should be handled with aseptic precautions. If the seam of the sterile package is broken, the product should be discarded. A discarded or removed IUS should be treated as medicinal waste, since it may contain hormone remnants. Each pack contains one intrauterine system.

Special instructions for insertion are in the package.

MIRENA is packaged in a polyethylene terephthalate glycol (PETG) sachet sealed with a peelable polyethylene film.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

24 July 2000

DATE OF MOST RECENT AMENDMENT

21 July 2017

® Registered Trademark of the Bayer Group, Germany