

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-oestrogenic 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 uterine cavity.

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 anti-oestrogenic effects. The anti-oestrogenic activity of levonorgestrel is not the result of direct oestrogen antagonism, since levonorgestrel does not bind to the oestrogen receptor *in vitro*, but the result of modification of peripheral oestrogenic 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 oestrogen 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 fertilisation. 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/amenorrhoea in others. Amenorrhoea is due to the local effect of levonorgestrel on the endometrium, which under strong local suppression does not proliferate in response to oestrogen. 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 oligomenorrhoea or amenorrhoea.

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 amenorrhic.

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.

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).

Menorrhagia

MIRENA can be successfully used in the treatment of idiopathic menorrhagia where no underlying pathology causing excessive bleeding can be found (see CONTRAINDICATIONS). In menorrhagic women, the 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. Compared to endometrial ablation or resection, MIRENA demonstrated equal efficacy in reducing the menstrual blood loss up to two years. 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. 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 increases the concentration of blood ferritin and haemoglobin. 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 oestrogen treatment when administering oestrogen either orally or transdermally. The observed hyperplasia rate under oestrogen 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.

The concomitant oestrogens used in the HRT studies were oral continuous estradiol valerate 2 mg/24 hours, continuous transdermal estradiol 50 microgram/24 hours, oral conjugated equine oestrogen 0.625, 1.25 mg/day oestradiol implants 36 microgram/24 hours and oestradiol 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

The active ingredient of MIRENA is levonorgestrel. Levonorgestrel is directly released into the uterine cavity. The in vivo release rate of levonorgestrel is initially approximately 20 microgram/24 hours and declines to 10 microgram/24 hours after five years.

Absorption

Following insertion, levonorgestrel is released from the IUS into the uterine cavity without delay based on serum concentration measurements. The high local drug exposure in the uterine cavity 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).

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 (25th to 75th percentiles: 151 picogram/mL to 264 picogram/mL) at 6 months to 194 picogram/mL (146 picogram/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 (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 oestrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approx. 478 picogram/mL (25th to 75th percentiles: 341 picogram/mL to 655 picogram/mL) due to the induction of SHBG by oral oestrogen treatment

Metabolism

Levonorgestrel is extensively metabolised. The major metabolites in the plasma are the unconjugated and conjugated forms of 3 α , 5 β -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.

Linearity/non-linearity

The pharmacokinetics of levonorgestrel is dependent on the concentration of SHBG which itself is influenced by oestrogens and androgens. During use of MIRENA, a mean SHBG decrease of about 30% was observed, which leads to a decrease of levonorgestrel in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly local action of MIRENA, no impact on the efficacy of MIRENA is expected.

Indications

Contraception

Treatment of idiopathic menorrhagia provided there is no underlying pathology.

Prevention of endometrial hyperplasia during oestrogen 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 oestrogen 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.

Paediatric Use

Safety and efficacy have not been established in women below 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 tumours.

Patients with Renal Impairment

MIRENA has not been studied in women with renal impairment.

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 oestrogen replacement therapy, MIRENA can be inserted during the last days of menstruation or withdrawal bleeding, or at any time in an amenorrhic 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 oestrogen 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 or other surgical intervention.

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
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 tumor
Hypersensitivity to the active substance or to any of the excipients

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
- acute venous thromboembolism.

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

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

Current evidence indicates that oestrogen replacement therapy should only be used short-term and that in most circumstances, the risk of long-term oestrogen 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 oestrogen replacement therapy, please refer to the information contained in the Data Sheet for oestrogen-containing preparations. In particular all prospective and current users of oestrogen-replacement preparations should be advised of the risks and benefits of treatment and the need for treatment should be reviewed frequently.

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 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 oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. As 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 oestrogen 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 Data Sheet of the oestrogen replacement therapy should also be consulted for additional information.

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/amenorrhoea

In a study with women of reproductive age using MIRENA, oligomenorrhea and amenorrhea developed gradually in 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 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 oestrogen 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.

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 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, 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 may be indicative of a perforation. Should a perforation occur, the intrauterine 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 1). These risk factors were independent of the type of IUD inserted.

Table 1: 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 ectopic pregnancy should be considered in the case of lower abdominal 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.

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 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 possibility of expulsion or perforation should be considered. 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.

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. 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 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 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.)

The use of MIRENA during an existing or suspected pregnancy is contraindicated (see CONTRAINDICATIONS). 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 virilising 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 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.

Effects on the Ability to Drive and Use Machinery

Not known

PRECLINICAL SAFETY DATA

Levonorgestrel is a well-established progestogen with anti-oestrogenic 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

The majority of women experience changes in menstrual bleeding pattern after insertion of MIRENA. During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after postmenstrual insertion of MIRENA, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, 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 oestrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

The frequencies of adverse reactions reported with MIRENA are summarised in the table below. 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 table below reports adverse reactions by MedDRA system organ class (MedDRA SOCs). The frequencies are crude incidences of the events observed in clinical trials in the indications “contraception” and “idiopathic menorrhagia”, including 5091 women and 12,101 woman-years.

Adverse reactions in clinical trials in the indication “prevention of endometrial hyperplasia during oestrogen replacement therapy” (including 514 women and 1218.9 woman-years) were observed at a similar frequency unless specified by footnotes.

Table 2: Adverse reactions reported in clinical trials with MIRENA

System Organ Class	Very Common	Common	Uncommon	Rare
Psychiatric Disorders		Depressed mood/Depression Nervousness	Altered mood	

System Organ Class	Very Common	Common	Uncommon	Rare
		Decreased libido		
Nervous System Disorders	Headache	Migraine		
Gastrointestinal Disorders	Abdominal /pelvic pain	Nausea	Abdominal distension	
Skin and Subcutaneous Tissue Disorders		Acne Hirsutism	Alopecia Pruritis Eczema	Rash Urticaria
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 expulsion (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 conditions.

* 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 WARNINGS AND 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.

Breast Disorders

The risk of breast cancer is unknown when MIRENA is used in the indication “prevention of endometrial hyperplasia during oestrogen replacement therapy”. Cases of breast cancer have been reported in MIRENA users (frequency unknown, see WARNINGS AND PRECAUTIONS).

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 WARNING AND PRECAUTIONS).

Investigations

Blood pressure increased

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, carbamazepine) 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

Special conditions for storage

Store the product below 25°C.

Medicine Classification

Prescription Medicine

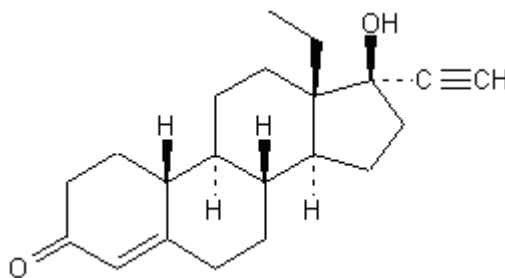
Package Quantities

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, 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 13 β -ethyl-17 β -hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one. The CAS registry number for levonorgestrel is 797-63-7.



Chemical Formula: C₂₁H₂₈O₂

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

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
AUCKLAND 0627

150420 MIRENA DS

Free phone: 0800 233 988

Date of Preparation

20 April 2015