NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MIRENA 52 mg intrauterine contraceptive device (release rate: 20 microgram/24 hours)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

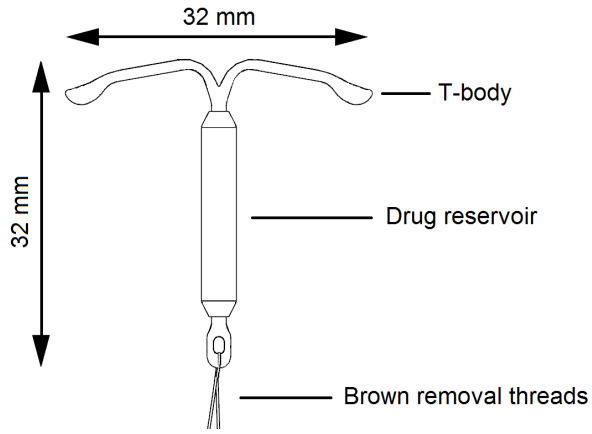
Levonorgestrel 52mg.

The average in vivo release rate is 20 microgram/ day during the first year. For details of release rates, see Section 5.2.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

MIRENA 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 white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Brown coloured removal threads are attached to the loop. The T-body of MIRENA contains barium sulfate, which makes it visible in X-ray examination. The IUS and inserter are essentially free from visible impurities.



4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception

Treatment of idiopathic menorrhagia provided there is no underlying pathology.

Prevention of endometrial hyperplasia during estrogen replacement therapy

4.2 Dose and method of administration

MIRENA is inserted into the uterine cavity. It has been shown to be effective for up to 8 years for contraception, and up to 5 years for the indications of idiopathic menorrhagia, and protection from endometrial hyperplasia during estrogen replacement therapy. (see section 5.1 PHARACODYNAMIC PROPERTIES – Clinical trials).

For timing regarding removal/ replacement, see section “Removal/ Replacement”

The *in vivo* levonorgestrel release rate 24 days after insertion is approximately 21 µg/day decreasing continuously to approximately 19 µg/day after 1 year, to 11 µg/day after five years and to 7 µg/day after 8 years of use.

The average daily levonorgestrel release rates are approximately 20 µg/day during the first year, 15 µg/day during the first 5 years and 13 µg/day over the complete 8 year period of use. 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.

4.2.1 Medical examination/consultation

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 should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional’s evaluation. 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.

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.

4.2.2 Insertion and removal/replacement

- Insertion:

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, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

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.

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.

- Removal/replacement:

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.

- Contraception:

The intrauterine system should be removed or replaced after 8 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 within 7 days of the onset of menstruation in women of reproductive potential, provided the woman is experiencing regular menses. If the intrauterine system is removed at some other time during the cycle or the woman does not experience regular menses and the woman has had intercourse within a week, she is at a risk of pregnancy. To ensure continuous contraception, a new system should be immediately inserted or an alternative method should have been initiated.

- Idiopathic menorrhagia

The system should be removed or replaced in case symptoms of idiopathic menorrhagia or dysmenorrhea return. If symptoms have not returned after 5 years of use, continued use of the system may be considered. Remove or replace after 8 years at the latest.

- Protection from endometrial hyperplasia during estrogen replacement therapy

The system should be removed or replaced after 5 years

4.2.3 Special populations

4.2.3.1 Paediatric population

Safety and efficacy have not been established in women below reproductive age. There is no relevant indication for the use of MIRENA before menarche.

4.2.3.2 Elderly

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

4.2.3.3 Hepatic impairment

MIRENA is contraindicated in women with acute liver disease or liver tumours.

4.2.3.4 Renal impairment

MIRENA has not been studied in women with renal impairment.

4.3 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

4.4 Special warnings and precautions for use

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 in blood pressure
- severe arterial disease such as stroke or myocardial infarction
- acute venous thromboembolism.

Previous studies indicate that an increased number of sexual partners may increase susceptibility to sexually transmitted infections (see Section 4.4.5).

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 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, please refer to the information contained in the Data Sheet 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.

4.4.1 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.

4.4.2 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.

4.4.3 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. 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 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 Data Sheet of the estrogen 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.

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.

4.4.4 Infrequent bleeding/amenorrhoea

In a study with women of reproductive age using MIRENA, oligomenorrhea (infrequent bleeding) and amenorrhea developed gradually in 57% and 16% of women, respectively, at the end of the first year of use. By the end of Year 8 of MIRENA use, infrequent bleeding and amenorrhoea are experienced by 26% and 34% of MIRENA users, respectively

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.

4.4.5 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.

4.4.6 Expulsion

Symptoms of the partial or complete expulsion of any intrauterine device 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 ultrasound 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. As MIRENA decreases menstrual flow, increased menstrual flow may be indicative of an expulsion.

Risk of expulsion is increased in:

- Women with history of heavy menstrual bleeding.
- Women with greater than normal BMI at the time of insertion; this risk increases gradually with increasing BMI.

Counsel the woman on possible signs of expulsion and instruct her on how to check the threads of MIRENA. Advise her to contact her doctor if the threads cannot be felt and avoid intercourse or use a barrier contraceptive (such as condoms) until the location of MIRENA has been confirmed.

Partial expulsion may decrease the effectiveness of MIRENA.

A partially expelled MIRENA should be removed. A new system can be inserted at the time of removal, provided pregnancy has been excluded.

4.4.7 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) with a 1 year observational period, the incidence of perforation was 1.3 (95% CI: 1.1-1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1000 insertions in the MIRENA cohort and 1.1 (95% CI: 0.7-1.6) per 1000 insertions in the copper IUD cohort. Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women using MIRENA or copper IUD), the incidence of perforation detected at any time during the entire 5-year period was 2.0 (95% CI: 1.6–2.5) per 1000 insertions.

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 confirmed in the subgroup followed up for 5 years. Both risk factors were independent of the type of IUD inserted.

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

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI: 3.9-7.9; n=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 Section 4.2.1), which may be adapted as clinically indicated in women with risk factors for perforation.

4.4.8 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. 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.

4.4.9 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.

4.4.10 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.

4.4.11 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.

4.5 Interaction with other medicines and other form of interaction

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, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John’s wort.

The influence of these medicines 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 progestin.

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.

4.6 Fertility, pregnancy and lactation

4.6.1 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.

4.6.2 Pregnancy

Pregnancy Category B3.

The use of MIRENA during an existing or suspected pregnancy is contraindicated (see Section 4.3). 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. Ectopic pregnancy should be excluded. 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. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

There have been isolated cases of masculinisation of the external genitalia of the female fetus following local exposure to levonorgestrel during pregnancy with an LNG-IUS in place.

4.6.3 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.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

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 was 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.

By the end of Year 8 of MIRENA use, prolonged bleeding and irregular bleeding were experienced by 3% and 10% of MIRENA users, respectively; amenorrhoea occurred in 34 %, and infrequent bleeding in 26% of MIRENA users.

When MIRENA is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

4.8.2 Tabulated list of adverse reactions

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 estrogen 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	Unknown
Immune System disorders				Hypersensitivity including rash, urticaria and angioedema
Psychiatric Disorders		Depressed mood/Depression Nervousness 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	
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)	Uterine perforation***	
Investigations				Blood pressure 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 a large, prospective, comparative, non-interventional cohort study in IUD users which showed that breastfeeding at the time of insertion and insertion up to 36 weeks

after giving birth are independent risk factors for perforation (see Section 4.4.7 Perforation). In clinical trials with MIRENA that excluded breastfeeding women, the frequency of perforation was "rare".

A separate study with 362 women who have used Mirena for more than 5 years showed a consistent adverse reaction profile in Years 6 through 8.

4.8.3 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 estrogen replacement therapy”. Cases of breast cancer have been reported in MIRENA users (frequency unknown, see Section 4.4).

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 Section 4.4).

Investigations
Blood pressure increased

4.8.4 Reporting of suspected adverse reactions

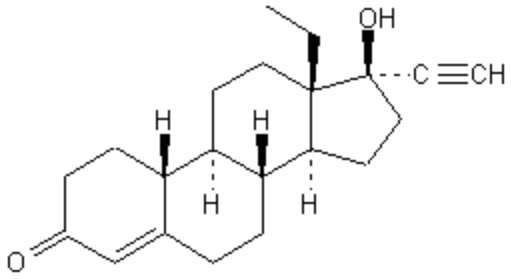
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to pophealth.my.site.com/carmreportnz/s/.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plastic IUD with progestogen
ATC Code: G02BA03

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

5.1.1 Mechanism of action

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 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-estrogenic effects. The anti-estrogenic 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.

5.1.2 Pharmacodynamic effects

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 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/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.

5.1.3 Clinical efficacy and safety

5.1.3.1 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 contraceptive efficacy during extended use beyond 5 years has been studied in the Mirena Extension trial with 362 women using Mirena, with 221 women completing Year 8 of the study. During Years 6 to 8 of Mirena use, the Pearl Index was 0.28 [95% CI (0.03,1.000].

The contraceptive efficacy of MIRENA up to 8 years, when inserted according to the insertion instructions, is presented in table 3 below.

Table 3: Contraceptive efficacy

Year	Cumulative Failure Rate (%)* (95% CI)	Pearl Index (95% CI)
Contraceptive Efficacy during Years 1 to 5 (N=3330, Pooled data of contraceptive trials up to 5 years)		
Year 1	0.20 (0.09, 0.46)	0.21 (0.08, 0.45)
Year 1 to 5	0.71 (0.37, 1.33)	
Contraceptive Efficacy during Years 6 to 8 (N=362, Mirena Extension Trial)		
Year 6	0.29 (0.04, 2.05)	0.34 (0.01, 1.88)
Year 7		0.40 (0.01, 2.25)
Year 8		0.00 (0.00, 1.90)
Year 6-8	0.68 (0.17, 2.71)	0.28 (0.03, 1.00)

***** Kaplan-Meier estimate

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).

5.1.3.2 Menorrhagia

MIRENA can be successfully used in the treatment of idiopathic menorrhagia where no underlying pathology causing excessive bleeding can be found (see Section 4.3). 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.

5.1.3.3 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 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 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.

5.2 Pharmacokinetic properties

5.2.1 Absorption

Following insertion, levonorgestrel is released from the IUS into the uterine cavity without delay based on serum concentration measurements. More than 90% of the released levonorgestrel is systemically available.

After insertion of MIRENA, levonorgestrel is detectable in serum/plasma after 1 hour. The maximum concentration is reached within 2 weeks after insertion and amounts to about 180ng/L (CV 38.3%).
In correspondence with the declining release rate, the geometric mean serum/plasma concentration of levonorgestrel declines continuously as shown in table 4:

Table 4: Total LNG plasma concentrations

Time after insertion	Total LNG plasma concentrations [ng/L] (geometric CV%)
24 days	175 (37.6)
2 months	169 (37.1)
1 year	159 (37.4)
3 years	139 (37.8)
5 years	123 (38.2)
8 years	100 (39.9)

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).

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 approx. 478 picogram/mL (25th to 75th percentiles: 341 picogram/mL to 655 picogram/mL) due to the induction of sex hormone binding globulin (SHBG) by oral estrogen treatment.

5.2.2 Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to SHBG. Less than 2% of the circulating levonorgestrel is present as free steroid. Levonorgestrel binds with high affinity to SHBG. Accordingly, changes in the concentration of SHBG in serum result in an increase (at higher SHBG concentrations) or in a decrease (at lower SHBG concentrations) of the total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 20~~-30~~% during the first two months after insertion of MIRENA, remained stable thereafter increasing only slightly until the end of the 8 years of use.

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.

5.2.3 Biotransformation

Levonorgestrel is extensively metabolised. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel. The available *in vitro* data suggest that CYP mediated biotransformation reactions may be of minor relevance for levonorgestrel compared to reduction and conjugation.

5.2.4 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.

5.2.5 Linearity/non-linearity

The pharmacokinetics of levonorgestrel is dependent on the concentration of SHBG which itself is influenced by estrogens and androgens. A decrease of SHBG concentration leads to a decrease of total levonorgestrel concentration 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.

5.3 Preclinical safety data

Levonorgestrel is a well-established progestogen with anti-estrogenic activity. The safety profile following systemic administration is well documented. Studies in monkeys with intrauterine delivery of levonorgestrel for 9 to 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, pharmacokinetics, toxicity, genotoxicity and carcinogenic potential of levonorgestrel.

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, rats, guinea pigs, rabbits and *in vitro* test systems.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylsiloxane/methylvinylsiloxane (cross-linked) elastomer, silica (colloidal anhydrous), polyethylene, barium sulfate, iron oxide Black C177499

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.6.1 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. For further information, see Section 4.2.2. Special instructions for insertion are in the package.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
P O Box 2825
Shortland Street
Auckland 1140
New Zealand
Free phone 0800 233 988

9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

10 April 2025

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Summary table of changes

Section changed	Summary of new information
4.2	Update of dosage section – contraception efficacy from 5 years to 8 years
4.4, 4.8, 5.1, 5.2	Update to include 8 years data information
2, 4.4	Editorial changes